

45th Annual

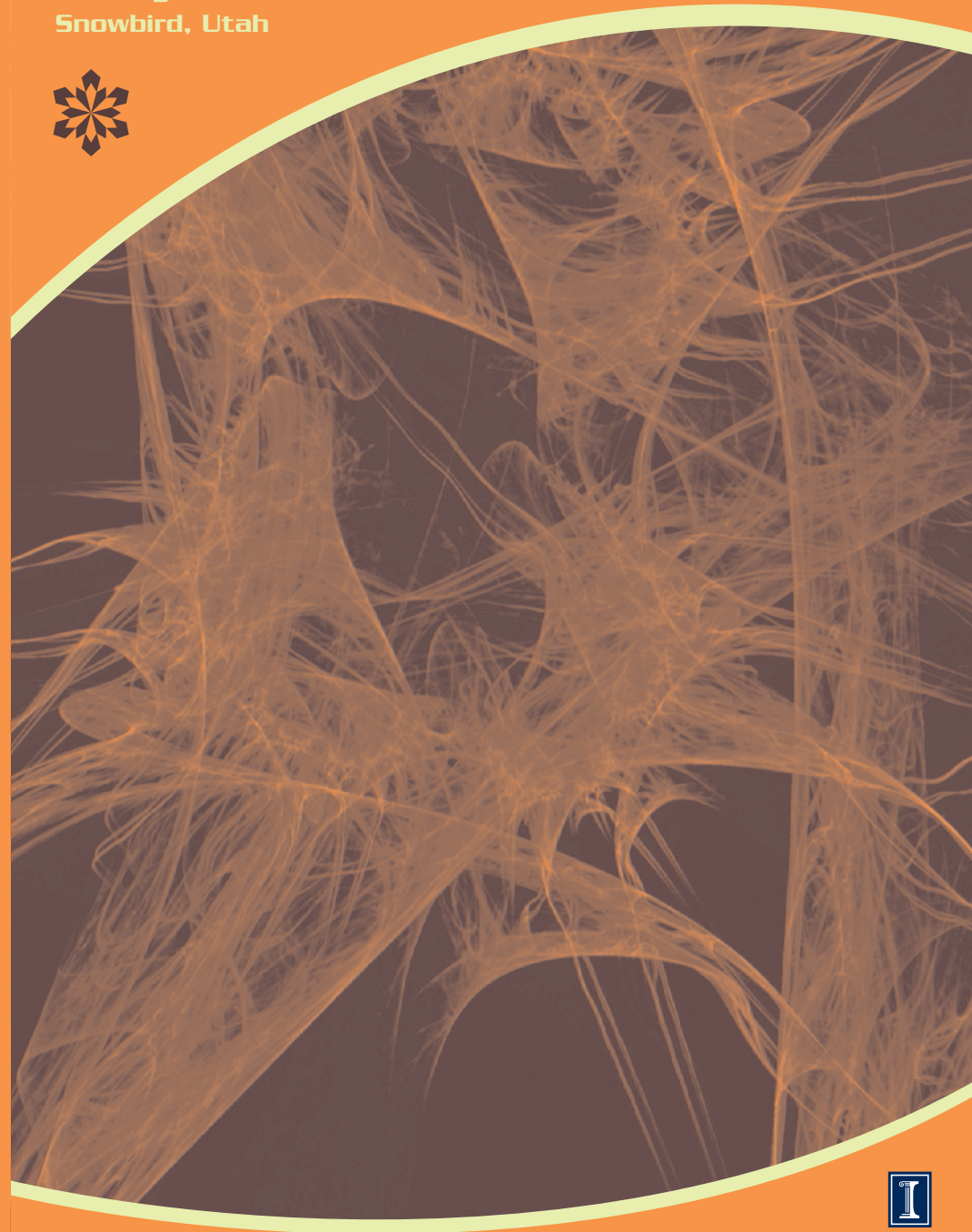
Winter Conference on Brain Research

January 21-26, 2012

Snowbird, Utah

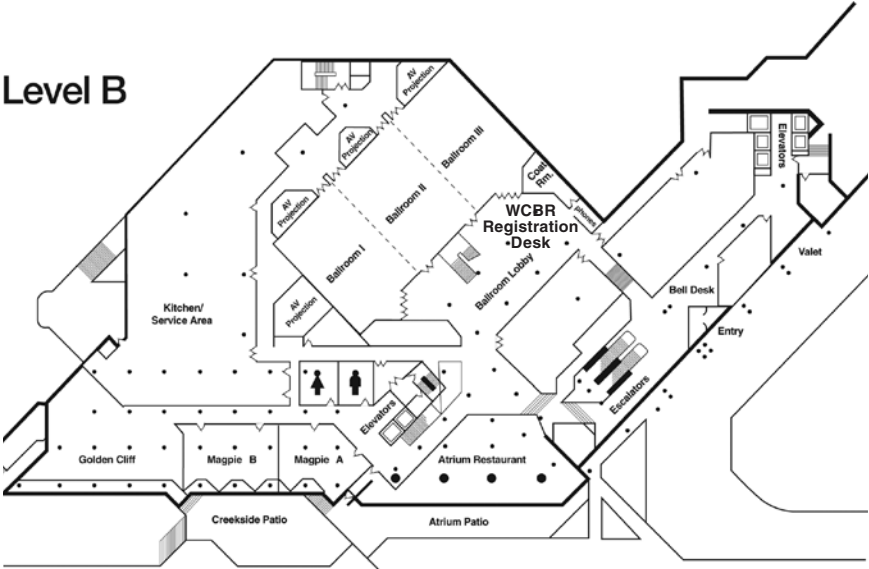


45th Annual Winter Conference on Brain Research 2012

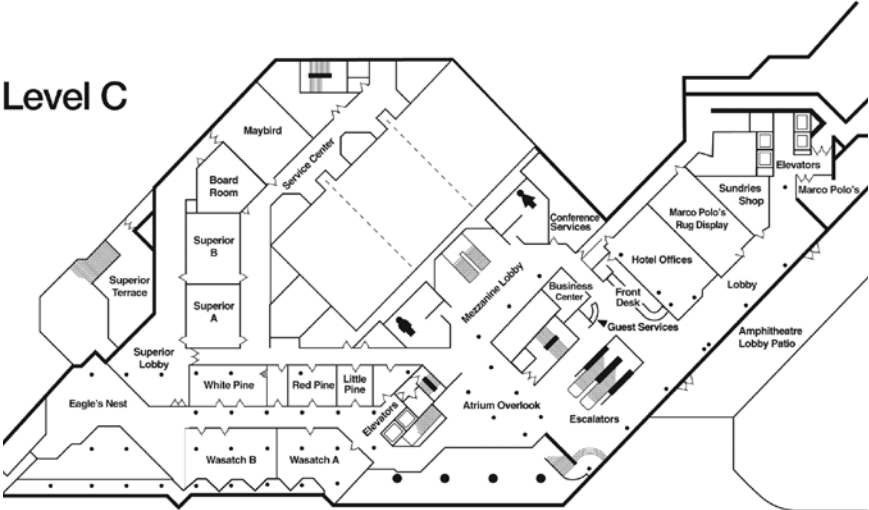


Cliff Lodge Meeting Rooms

Level B



Level C



Welcome to the Forty-Fifth Annual Winter Conference on Brain Research

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

The **Opening Breakfast** on Sunday will feature our keynote speaker, **Carol Barnes, PhD**. Dr. Barnes is a world leader in the study of the neural mechanisms of memory loss during normal brain aging, with more than 210 publications and numerous grants. Dr. Barnes is actively involved with the Arizona Alzheimer's Consortium and is a past-president (2005) of the 41,000-member Society for Neuroscience, an elected Fellow of the American Association for the Advancement of Science, and an Elected Foreign Member of the Royal Norwegian Society of Sciences and Letters. As president of the Society for Neuroscience, Dr. Barnes invited the Dalai Lama to be the speaker for the Dialogues between Neuroscience and Society; and she was instrumental in broadening the participation of non-US members in the SfN. This later effort continues to be an interest of Dr. Barnes, and the topic of her address to the WCBR, "Society for Neuroscience as a global force in brain science: What are SfN's actual constituencies?"

We have a full week of science and socializing planned. We will again host two activities that are designed to educate the lay public. On Monday night, WCBR will hold a **Town Meeting Lecture**, organized again this year by Karen Greif, to be held in the Golden Cliff room. Our speaker is John Mendelson; his topic is "Talking about drugs with kids—What to say and why to say it." All WCBR attendees and their families are welcome to join the lay public at the lecture and

reception. WCBR scientists also provide **School Outreach** sessions, organized by Frank Welsh, throughout the week in the local elementary, middle, and high schools. You are all invited to the **Special Poster Session** on Tuesday evening featuring top poster abstract submissions from new investigators and light refreshments. You are encouraged to engage in discussions with poster presenters, as well as corporate exhibitors. Exhibitors also sponsor the afternoon breaks, so please visit exhibitor booths throughout the week. Plan to join us at Wednesday's **Mountain Lunch** to be held at Gad Valley. The **Smitty Stevens Memorial (NASTAR) Ski Race** will occur on the Gad Valley slope on Wednesday. Please be sure to attend the **Business Meeting** on Wednesday following the afternoon sessions, as we will be holding elections for facilities chair-elect, program chair-elect, and board members. Additionally, we will be discussing the program, budget, and future meeting sites. The board members are important for WCBR governance; we encourage you to nominate yourself or a colleague for open board positions in clinical, cell/molecular, or systems/behavioral neuroscience. We will close the week on Thursday night with the **Annual Banquet**, where we will announce awards for the special poster session and the ski race, as well as let our hair down dancing to live music.

As an all-volunteer organization, please join me in thanking Paul Phillips, program chair, and his committee members for an outstanding scientific program. We thank Tom Hyde, facilities chair, for the meeting venue and organization. Thanks to Paula Dore-Duffy and Denson Fujikawa, who have solicited support from the many exhibitors at the conference and advertisers in the program. Behind the scenes, Gretchen Snyder and George Wilcox, as fellowship co-chairs, have worked hard to identify exceptional Travel Fellows and matched them with WCBR mentors. Jacqueline McGinty keeps us on solid financial ground as WCBR treasurer. Lastly, we thank the current members of the board of directors and Past WCBR Conference Chair Kimberly Topp for guidance throughout the year; and Michelle Chappell at the University of Illinois for limitless energy, historical memory, and professional meeting organization.

Enjoy the meeting, your colleagues, and the snow!

Jill Becker
Conference Chair

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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:

	<i>Morning</i>	<i>Afternoon</i>
Saturday 1/21	8:00 a.m.–12:00 p.m.	3:30–9:00 p.m.
Sunday 1/22	6:30–10:00 a.m.	3:30–7:00 p.m.
Monday 1/23	7:00–10:00 a.m.	3:30–6:45 p.m.
Tuesday 1/24	7:00–10:00 a.m.	3:30–6:00 p.m.
Wednesday 1/25	7:00–10:00 a.m.	3:30–5:30 p.m.
Thursday 1/26	7:00–10:00 a.m.	

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

Poster Session 1, Sunday

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

Poster Session 2, Monday

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

Poster Session 3, Tuesday

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

Poster Session 4, Wednesday

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

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

Exhibits and Lounge are in Ballroom 2 & 3. Refreshments are provided 3:30 to 4:30 p.m., Sunday through Wednesday. Exhibitor setup is Sunday, January 22, 12:00–3:00 p.m. All exhibitors should be packed up by 2:00 p.m. on Thursday, January 26.

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

Monday through Thursday, breakfast will be available from 6:30 to 9:00 a.m. at the Atrium (Cliff Lodge Level B), 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 **only during desk hours.**

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



Committees

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Patricio O'Donnell,
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Denson Fujikawa

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Town Meeting Coordinator

Karen Greif

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Conference Arrangements

Michelle Chappell
Online & Continuing
Education
University of Illinois
901 W. University Ave,
Suite 101
Urbana, IL 61801
Phone 217-333-2880
Fax 217-333-9561
E-mail:
winterbrain@ad.uiuc.edu

Travel Fellowship Program

Fellowship Committee

Gretchen L. Snyder,
Co-Chair
George Wilcox,
Co-Chair
Karen Greif
Kimberly Topp

2012 Fellowship Awardees

Devin Mueller,
Ann Kelly Memorial
Travel Fellow
Matthew Banghart
Jeff Beeler
William Birdsong
Christine Clementson
Herb Covington
Ashley Fricks-Gleason
Kasper Hansen
Giovanni Hernandez
Jessica Loweth
Martine Mirrione
Sean Ostlund
Amynah Pradhan
Jason Shepherd
Dennis Sparta
Tuan Trang
Kay Tye
Sara Ward

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David Baker
Brian Baldo
Jill Becker

Michael V L Bennett
Stephanie Borgland
Katherine Burdick
Joseph Cheer
Lique Coolen
Brian Cummings
Michael Davis
Sonsoles De Lacalle
Luis De Lecea
Ksren Gale
Amelia Gallitano
Herbert Geller
Francois Georges
Edward Hall
Xue Han
Eric Harris
Fritz Henn
Elizabeth Jonas
Leonard Kaczmarek
Kristen Keefe
Gonzalo Laje
Barry Levin
Michael Levine
Barbara Lipska
Joaquin Lugo
Wendy Macklin
Juan Carlos Marvizon
Jacqueline McGinty
John Mendelson
Paul Micevych
David Naylor
Patricio O'Donnell
Tulen Pekny
Elior Peles
Paul Phillips
Margaret Rice
Steve Richardson
Susanna Rosi
Wolfgang Sadee
Todd Scheuer

Barry Setlow
Donald Stein
David Stellwagen
Garret Stuber
Michael Sutton
Jennifer Thomas
Kathy Toreson
Ramon Trullas
Kuei Tseng
Kay Tye
Edward Wagner
Claude Wasterlain
George Wilcox
James Zadina

Fellowship Sponsors

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



Gold Sponsors (\$500-\$100)

Jill Becker
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(up to \$49)

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Todd Scheuer



Exhibitors

Association Book Exhibit

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

CWE, Inc.

315 E. County Line Road
Ardmore, PA 19003
Contact: Benjamin Bedard
Tel 610-642-7719
bedard.ben@gmail.com

Fine Science Tools

373-G Vintage Park Dr
Foster City, CA 94404
Contact: Christina Callanta
Tel 800-521-2109
ccallanta@finescience.com

MBF Bioscience

185 Allen Brook Lane, Suite 101
Williston, VT 05495
Contact: Geoff Greene
Tel 802-288-9290
geoff@mbfbioscience.com

Olympus America Inc.

3500 Corporate Parkway
Center Valley, PA18034
Contact: Kathleen Karmel
Tel 801-209-8472
kathleen.karmel@olympus.com

SAGE Labs

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

Stoelting

620 Wheat Lane
Wood Dale, IL 60191
Contact: Trent Lund
Tel 630 860 9700
Fax 630 860 9775
trent@stoeltingco.com

Special Events

Saturday, January 21

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

Sunday, January 22

Conference Breakfast and Plenary Address • Ballroom

7:00–8:30 a.m. • Breakfast

8:00–9:30 a.m. • Plenary Address

The plenary keynote address is presented by

Carol A. Barnes, PhD, Regents' Professor of Psychology and Neurology, Director, Evelyn F. McKnight Brain Institute, Endowed Chair for Learning and Memory in Aging, University of Arizona

*Society for Neuroscience as a global force in brain science:
What are SfN's actual constituencies?*

Dr. Barnes is a world leader in the study of the neural mechanisms of memory loss during normal brain aging, with more than 210 publications and numerous grants. Dr. Barnes is actively involved with the Arizona Alzheimer's Consortium, and is a past-president (2005) of the 41,000 member Society for Neuroscience, an elected Fellow of the American Association for the Advancement of Science, and an Elected Foreign Member of the Royal Norwegian Society of Sciences and Letters.

As President of the Society for Neuroscience, Dr. Barnes invited the Dalai Lama to be the speaker for the Dialogues between Neuroscience and Society, and she was instrumental in broadening the participation of non-US members in the SfN. This later effort continues to be an interest of Dr. Barnes, and the topic of her address to the WCBR.

The Society for Neuroscience began in 1969 as a small group of brain scientists (500 members). Over the past 42 years, it has grown to a 41,000-person Society with 39% of its members residing across 22 countries outside the United States. It took the Society 16 years to elect a woman president, 33 years to eliminate the "Foreign Member" membership category, 32 years before it had its first chapter outside North America, 37 years before it built a "green building" for its headquarters, and 36 years before it

began formally to reach outside its interdisciplinary boundaries to explore how neuroscience can be inspired by science and thought generated by other disciplines. What's next?

Monday, January 23

First Meeting of the Board of Directors • 6:30–8:30 a.m. • White Pine

Town Meeting • 7:00–8:30 p.m. • Golden Cliff

Attendance is open to all.

“Talking about drugs with kids—What to say and why to say it”

John Mendelson, MD, Addiction and Pharmacology Research Lab,
California Pacific Medical Center

Tuesday, January 24

Breakfast for Travel Fellows Meeting • 6:30–7:30 a.m. • Aerie Restaurant
(Cliff Lodge Level 10)

Memorial Panel • 9:45–11:15 am • Ballroom 1

In honor of Bart Hoebel: A giant for 50 years in the field of food and drug reward

Chair: Sarah Leibowitz

Presenters: Friedbert Weiss, George Koob, Charles O'Brien

Fifty years ago, Bart Hoebel at Princeton University published his first paper, “Hypothalamic control of feeding and self-stimulation,” in *Science*. Since that time, Bart has been a pioneer and leader in the field of food and drug reward and has contributed enormously to our understanding of the diverse neurochemical mechanisms in the brain that are involved in mediating reward pathways. He has also been exceptional in attending all of the WCBR meetings since the founding of this conference in 1968. The members of this panel, which is dedicated to Bart, will describe their recent studies on food and drug reward as they relate to Bart’s research, focusing on different neurochemical systems that are known to control both food and drug abuse. Leibowitz will describe evidence, obtained in collaboration with Bart, for positive feedback loops or “vicious cycles” involving various orexigenic peptides, in the hypothalamus and mesocorticolimbic regions, which promote the ingestion of fat, sugar, and alcohol and are overactive in animals with an inherent predisposition to overconsume these substances. Koob will present new results on the dark side of drug and food addiction and will relate his findings to Bart’s acetylcholine

opponent process in the nucleus accumbens. Weiss will describe his recent findings on the orexin/hypocretin system as it controls natural and drug reward and will link this evidence to Bart's view of "integrative neuropeptides." O'Brien, building on Bart's animal studies of opioid peptides, will describe his current studies in humans, showing opioids to be activated by alcohol, especially in individuals with genetically determined sensitivity, and opioid antagonists to be an effective treatment for alcoholism. These four presentations underscore the diversity of brain mechanisms mediating different components of the reward pathway, as well as the diversity of Bart's research as a towering figure in this field.

Special Poster Session • 6:30–8:30 p.m. • Ballroom 2 & 3

The top-ranked posters submitted by junior investigators will be on display, Tuesday from 6:30 to 8:30 p.m. in a special session, with wine and cheese provided. Awards will be selected, including a "Best Poster" award. A grand prize will be given to the best poster, and several prizes will also be given to runners-up. The awards will be announced at the Closing Banquet on Thursday, January 26.

Wednesday, January 25

Smitty Stevens Memorial (NASTAR) Ski Race • 10:00–11:30 a.m. • Gad Valley

NASTAR registration cards to be completed no later than Monday, January 23, 8:00 a.m., at the WCBR Information Desk or online at www.nastar.com.

Mountain Lunch • 11:30 a.m.–2:00 p.m. • Gad Valley

Non-skiers will take a shuttle bus (red and blue) from Snowbird Center to Gad Valley. The lunch is outdoors; please dress accordingly.

Skiers, lunch is at the bottom of Gad Valley.

Required lunch ticket is in your registration packet.

Business Meeting • 6:30 p.m. • Ballroom 1

Attendees will vote on the Program and Facilities Chair-Elect, board member positions, and discuss locations of future meeting sites, along with other business items.

All are welcome and encouraged to attend.

Thursday, January 26

Second Meeting of the Board of Directors • 6:30–8:30 a.m. • White Pine

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

Banquet and Dance • 7:30 p.m. • Ballroom

Required ticket is in your registration packet.



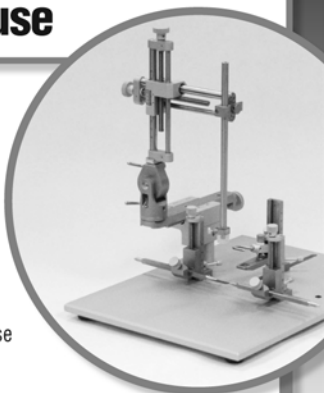
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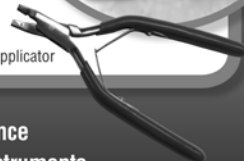
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Program

Preamble to the Program

The 2012 WCBR Program consists of panels and posters. Please consult the program book and posted announcements for details regarding the scientific presentations as well as information regarding the School Outreach program and the Town Meeting.

Sunday, January 22

7:00 a.m.

Breakfast • Ballroom

8:00 a.m.

Plenary Address • Ballroom

“Society for Neuroscience as a global force in brain science: What are SfN’s actual constituencies?”

Carol A. Barnes, PhD

3:30–4:30 p.m.

Exhibits and Posters • Ballroom 2 & 3

4:30–6:30 p.m.

1. Panel • Ballroom 1

Controlling the brain with light: An optogenetic approach to study the neural circuit basis of behavior

Kay Tye, Garret Stuber, Melissa Warden, **Chair: Donna Calu**

2. Panel • Magpie

Pharmacology gone wild in the world of addiction neurobiology

Chair: Christopher Evans, Amynah Pradhan, Mark von Zastrow, Ken Mackie, Charles Chavkin

3. Panel • Wasatch

Neurodevelopment, neurodegeneration, and cognition in psychiatric disorders across the lifespan

Anil Malhotra, Katherine Burdick, **Chair: Jeremy Koppel**, Thomas Hyde

4. Panel • Maybird

Calcium channel regulation and presynaptic plasticity

Chair: William Catterall, Thomas Sudhof, Karina Leal, Diane Lipscombe

Sunday, January 22, continued

5. **Panel • Superior A**
Effects of insulin in the mesolimbic dopamine system
Chair: Stephanie Borgland, Aurelio Galli, Margaret Rice, Tommy Pattij
6. **Panel • Superior B**
Can we really figure out repair in the adult by studying development?
Chair: Wendy Macklin, Jonah Chan, Steven Fancy, Teresa Wood, Sybil Stacpoole

8:30–10:00 p.m.

7. **Panel • Ballroom 1**
Are all addictions the same? A traditional symposium
Chair: John Mendelson, Jacqueline McGinty, Ghazaleh Sadri-Vakili
8. **Panel • Magpie**
Neuroprotection, rehabilitation, and regeneration of the alcohol-exposed CNS
Chair: Jennifer Thomas, Alexandre Medina, Kim Nixon

9. **Panel • Wasatch**
Cannabinoids and schizophrenia: What's pot got to do with it?
Chair: Joseph Cheer, Roger Cachepe, Kuei Tseng, Deepak Dsouza
10. **Panel • Maybird**
NMDA receptor signaling: New turns and twists
Chair: R. Suzanne Zukin, Stephen F. Traynelis, Mark Dell'Acqua
11. **Panel • Superior A**
New ideas on chronic pain
Chair: Juan Carlos Marvizon, Ann Gregus, Lucy Vulchanova, Bradley Taylor
12. **Panel • Superior B**
Glial cells: An overlooked regulator of neural activity
Cagla Eroglu, Dorothy Schafer, David Stellwagen, Chair: David Baker

Monday, January 23

7:30–9:30 a.m.

13. Panel • Ballroom 1

Impaired neural plasticity and NMDA receptor hypofunction in schizophrenia: A challenge for more effective treatment

Chair: Joseph Coyle, Robert Schwarcz, Z. Jeff Daskalakis, Don Goff

14. Panel • Magpie

Challenges and opportunities in treatment discovery for nicotine dependence: An integrated perspective

Chair: Athina Markou, Phil Skolnick, Paul Kenny, Caryn Lerman

15. Panel • Wasatch

Modulation of dopamine neuron activity by afferents: Implications in reward

Chair: Kathy Toreson, Dennis Sparta, Carlos Paladini, Francois Georges

16. Panel • Maybird

Metabotropic glutamate receptor 4 (mGlu4) as a novel target for CNS drugs: From chemistry to behavior

Francine Acher, Dario Doller, Colleen Niswender, **Chair:** Andrzej Pilc

17. Panel • Superior A

For they don't know what they are doing: Enduring effects of early-life stimulant exposure

Barry Kosofsky, Pradeep Bhide, **Chair:** Heinz Steiner, Carlos Bolaños

18. Panel • Superior B

Glia: A nemesis in opioid use

Chair: Cathy Cahill, Tuan Trang, Kurt Hauser, Anna Taylor, Daniela Salvemini

3:30–4:30 p.m.

Exhibits and Posters • Ballroom 2 & 3

4:30–6:30 p.m.

19. Panel • Ballroom 1

Imaging the human dopamine system: An updated view of the inverted U

Chair: Elizabeth Tunbridge, Oliver Howes, Daniel Weinberger, Paul Phillips

20. Panel • Magpie

Stress, drugs, and alcohol: The adolescent brain on a poorly groomed slope

Cheryl McCormick, Frances Leslie, **Chair:** Josh Gulley, Christine Konradi

21. Panel • Wasatch

Genome sequencing of psychiatric disorders: An avalanche of new data

Chair: John Kelsoe, James Knowles, Gonzalo Laje, Anil Malhotra

22. Panel • Maybird

PICK1 is not picky: From synaptic plasticity to neuroendocrine secretion and male infertility

Kenneth L. Madsen, Richard L. Haganir, Jun Xia, **Chair:** Ulrik Gether

Monday, January 23, continued

23. Panel • Superior A

Neurotensin: Self-control neuropeptide and drug discovery target

Chair: Jerry Frankenheim, Glen Hanson, Mona Boules, Ricardo Cáceda, George Uhl

24. Panel • Superior B

Oligodendrocytes and CNS myelination: Molecular mechanisms regulating cellular morphology during development and disease

Chair: Babette Fuss, Donna Osterhout, Timothy Kennedy, Carmen Melendez, Pamela Knapp

7:00–8:30 p.m.

Town Meeting • Golden Cliff (Level B)

“Talking about drugs with kids—
What to say and why to say it”

John Mendelson, MD

8:30–10:00 p.m.

25. Panel • Ballroom 1

Regulation and function of adult neurogenesis

Chay T. Kuo, **Chair: Zhengui Xia**, Xinyu Zhao, Evan Y. Snyder

26. Panel • Magpie

Blast traumatic brain injury

C. R. “Dale” Bass, **Chair: Barclay Morrison**, David Meaney

27. Panel • Wasatch

Understanding and enhancing motor behavior with noninvasive brain stimulation for the benefit of healthy and stroke patients

Chair: Pablo Celnik, Giacomo Koch, Friedhelm Hummel

28. Panel • Maybird

Hemichannels in the nervous system: More than “half” the story?

Michael Bennett, Nanna MacAulay, **Chair: Bruce Ransom**

29. Panel • Superior A

Deciphering a paradox: The role of the serotonin_{2A} receptor in antipsychotic action

Chair: Amelia Gallitano, Caitlin McOmish, Javier González-Maeso, David Erritzoe

30. Panel • Superior B

New biological findings and treatment approaches in PTSD

Chair: Chris Reist, Michael Hollifield, Suzy Bird Gulliver, Michael Alkire

Tuesday, January 24

7:30–9:30 a.m.

31. Panel • Ballroom 1

**Magic bullets and arrows:
Biological approaches to treat
substance use disorders**

Chair: Phil Skolnick, Paul Pentel,
Paul Bremer, Stephen Brimijoin,
Tom Kosten

32. Panel • Magpie

**Homeostatic and reward
mechanisms involved in the neural
regulation of energy homeostasis
and obesity**

Chair: Barry Levin, Catherine
Kotz, Emily Noble, Brian Baldo

33. Panel • Wasatch

**New approaches to probe
pathology in the human brain**

Chair: Gregory Ordway, Scott
Russo, Stephen Ginsberg, Wolfgang
Sadee, Mirjana Maletic-Savatic

34. Panel • Maybird

**Dynamic regulation of
glutamatergic synapses: From
mechanisms to functional
consequences**

Chair: Andres Barria, Karen Zito,
Lu Chen, **Chair: Hey-Kyoung Lee**

35. Panel • Superior A

**The Habenula: At the crossroads
of circuits mediating addiction
and depression**

Martine Mirrione, Ramiro Salas,
Wayne Drevets, **Chair: Fritz Henn**

36. Panel • Superior B

**Encoding motivation and arousal
in the brain: Neuropeptide
regulation of catecholamine
systems**

Rita Valentino, **Chair: Julia Lemos**,
Luis de Lecea, Stephanie Borgland

9:45–11:15 a.m.

Special Session • Ballroom 1

**In honor of Bart Hoebel: A giant
for 50 years in the field of food and
drug reward**

Chair: Sarah Leibowitz, Friedbert
Weiss, George Koob, Charles
O'Brien

3:30–4:30 p.m.

Exhibits and Posters • Ballroom 2 & 3

4:30–6:30 p.m.

37. Panel • Ballroom 1

**To ski or not to ski: Dopamine's
role in value-guided decision
making**

Jeff Beeler, Sean Ostlund, **Chair:**
Paul Phillips, Saleem Nicola

38. Panel • Magpie

**Neuroepigenetic and neurotrophic
control of the prefrontal-
accumbens circuit in response to
stress and drugs**

Courtney Miller, Herb Covington,
Chair: Jacqueline McGinty,
Ghazaleh Sadri-Vakili

Tuesday, January 24, continued

39. Panel • Wasatch

Stem cell: From altered biology to cell-replacement therapy

Chair: Susanna Rosi, Fulton Crews, Miles Herkenham, Cesar Borlongan, Charles Limoli

40. Panel • Maybird

New insights to modulation of ionotropic glutamate receptor function

Frank Menniti, **Chair: Kasper B. Hansen**, David S. Bredt, Geoffrey T. Swanson

41. Panel • Superior A

Opioid receptors: Binding, activation, phosphorylation, and desensitization

Chair: John Williams, Michelle Zedlitz, William Birdsong, Matthew Banghart, Shane Hentges

42. Panel • Superior B

Alzheimer's disease: Pathology and treatment in animal models

Michael Kawaja, **Chair: Isabelle Aubert**, JoAnne McLaurin, Henriette van Praag

6:30–8:30 p.m.

Special Poster Session and Reception •
Ballroom 2 & 3



Wednesday, January 25

7:30–9:30 a.m.

43. Panel • Ballroom I

Integration of information in the nucleus accumbens and reward-based behaviors

Chair: Patricio O'Donnell, Bruce Hope, Garret Stuber, Gwendolyn Calhoon, Michael Cohen

44. Panel • Magpie

How drugs of abuse alter the function of metabotropic glutamate receptors: Behavioral and molecular evidence

Friedbert Weiss, Foster Olive, **Chair: Marek Schwendt**, John Q. Wang

45. Panel • Wasatch

Therapeutic roles of histone deacetylase (HDAC) inhibition in neurological disorders

Chair: Elizabeth Thomas, Santosh R. D'Mello, Curt Freed, Fred Maxfield, George Rogge

46. Panel • Maybird

Molecular mechanisms regulating synaptic signaling in health and disease

Chair: Josef Kittler, Katherine Roche, Roger Nicoll, Nicholas Brandon

47. Panel • Superior A

The locus coeruleus-norepinephrine system and stress: From behavioral flexibility to psychopathology

Rita Valentino, **Chair: Vaishali Bakshi**, David Devilbiss, David Morilak, **Chair: Craig Berridge**

48. Panel • Superior B

DAPleted: What does partial dopamine loss do to basal ganglia function?

Martin Darvas, Christopher Howard, **Chair: Kristen Keefe**, Jakob Dreyer

10:00–11:30 a.m.

Smitty Stevens Memorial Ski Race •
Gad Valley

11:30–2:00 p.m.

Mountain Lunch • Gad Valley

3:30–4:30 p.m.

Exhibits and Posters • Ballroom 2 & 3

4:30–6:30 p.m.

49. Panel • Ballroom 1

Is it all Mother's fault? Fetal human brain development and schizophrenia

Nenad Sestan, Carlo Colantuoni, Amanda Law, **Chair: Thomas Hyde**

50. Panel • Magpie

Behavioral disinhibition, drugs, and brain dysfunction: Chicken and egg in rat and human

Susan Young, **Chair: Thomas Crowley**, Kathryn Cunningham, Barry Setlow

51. Panel • Wasatch

Neurobiology of affective resilience: New insights from social defeat models

Chair: Olivier Berton, Richard Gustin, Vincent Vialou, Kafui Dzirasa

52. Panel • Maybird

Estrogenic modulation of metabotropic receptor function and the associated behaviors regulated by their activation

Jill Becker, Kevin Sinchak, **Chair: Edward Wagner**, Nancy Muma

53. Panel • Superior A

Cannabinoids and motivation: New insights on an old tale

Chair: Joseph Cheer, Tommy Pattij, Eliot Gardner, Sara Ward, Giovanni Hernandez

54. Panel • Superior B

Neuroinflammatory mediators and amphetamines: Beyond biogenic amines

Chair: Bryan Yamamoto, Gary Gudelsky, James O'Callaghan, Nicole Northrop, Jesus Angulo

6:30 p.m.

Business Meeting • Ballroom 1

All are welcome and encouraged to attend.

Thursday, January 26

7:30–9:30 a.m.

55. Panel • Ballroom 1

Frontal cortical limbic circuits impact your thinking about drinking

Chair: Fulton Crews, Theodora Duka, Dai Stephens, Olivier George

56. Panel • Magpie

Sex, drugs, and rocky road: Neurobehavioral similarities and differences between drug and nondrug reinforcers

Chair: Chris Olsen, Lique Coolen, Marilyn Carroll, Paul Kenny, Peter Thanos

57. Panel • Wasatch

Disorders of cognitive function: From genes to mechanisms

Chair: Albert Galaburda, Daniel Geschwind, Daniel Weinberger, Allan Reiss

58. Panel • Maybird

Regulation of AMPA-type glutamate-receptor activity and localization

Steven Tavalin, Richard Huganir,
Chair: Andres Maricq

59. Panel • Superior A

Opting for opsins: Problems and promises for manipulating neural circuits in vivo

Chair: Karen Gale, Kay Tye, Luis DeLecea, Xue Han, Patrick Forcelli

60. Panel • Superior B

Neuronal RNA regulation

Chair: Melissa Barker-Haliski, Nora Perrone-Bizzozero, Scott Barbee, Miles Wilkinson, Jean-Claude Lacaille

4:30–6:30 p.m.

61. Panel • Ballroom 1

Epigenetics in human brain

Chair: Joel Kleinman, Gustavo Turecki, Joel Kleinman, Rahul Bharadwaj, Carolina Montano

62. Panel • Magpie

The role of drug-cue memories in relapse: 1 problem, 4 neurotransmitter systems

Chair: Ashley Fricks-Gleason, Devin Mueller, Kathryn Cunningham, Kathryn Reissner

63. Panel • Wasatch

Neuroethological approach to behavioral choice

Todd Coleman, Björn Brembs, Michael Platt, **Chair:** Rhanor Gillette

64. Panel • Maybird

Homeostatic Plasticity: Single synapses to neural circuits

Jason Shepherd, Jessica Loweth, Jean-Claude Beique, **Chair:** Michael Sutton

65. Panel • Superior A

The neuroplasticity of chronic pain alters perception of reward

Andrea Hohmann, Carrie Wade, Zaijie Wang, **Chair: Carolyn Fairbanks**

66. Panel • Superior B

The immune system in CNS: Friend and foe?


Chair: Marcela Pekna, Christine Ekdahl Clementson, Alexander Stephan, Lisa Boulanger, Michal Schwartz

6:30 p.m.

Reception • Ballroom Lobby

7:30 p.m.

Banquet and Dance • Ballroom



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

Poster Session 1

Sunday, January 22 • Ballroom 2 & 3

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

- P1. The role of cortical dopamine 1 receptors in delayed discounting and its reversal with methylphenidate
Susan Andersen
- P2. Environmental enrichment: Differential effects of drugs on object recognition memory in rats
Arjan Blokland
- P3. Amyloid deposition is an immunosuppressive event
Carol Colton
- P4. Spreading convulsions, spreading depolarization, and epileptogenesis in human cerebral cortex
Jens Dreier
- P5. The role of neuronal nitric oxide synthase-containing striatal interneurons in methamphetamine-induced dopamine neurotoxicity
Ashley Fricks-Gleason
- P6. Characterization of neurons in the prefrontal cortex activated during persistent heroin craving in rats
Evan Goldart
- P7. Amelioration of motor neuron degeneration in cellular and animal models of amyotrophic lateral sclerosis by exendin-4
Nigel Greig
- P8. Dopaminergic modulation of cortical-striate circuits during positive and negative expectations
Henry Holcomb
- P9. Endogenous modulation of GABA(A) receptor function governs pathological sleepiness in the primary hypersomnias
Andrew Jenkins
- P10. Chronic L-DOPA treatment restores impaired basal ganglia gene expression in rats with methamphetamine-induced neurotoxicity
Kristen Keefe
- P11. Mechanosensation, TRP channels, and calcium signaling in glaucoma
David Krizaj
- P12. Phosphatase involvement in recovery from morphine desensitization in locus coeruleus neurons from morphine-tolerant rats
Erica Levitt
- P13. Alterations in mTOR pathway signaling following status epilepticus in immature vs. mature rats
Joaquin Lugo
- P14. Mouse model of L-DOPA-induced nigrostriatal neurodegeneration
Eugene Mosharov

P15. Investigating the dopamine D2 receptor (D2R) orthosteric binding site with analogues of sumanirole

Amy Newman

P16. Cerebral blood flow response to functional activation

Olaf B. Paulson

P17. Quantification and involvement of soluble GDNF receptor, GFR α -1, in dopamine regulation

Brandon Pruett

P18. High-throughput screening for allosteric modulators of the D2 dopamine receptor

David Sibley

P19. Both DGL α and DGL β regulate the production of 2-Arachidonoyl glycerol in autaptic hippocampal neurons

Alex Straiker

P20. Neuronal Pentraxin 1 regulates activity-dependent mitochondrial dynamics

Ramon Trullas

P21. Nitric oxide-mediated regulation of β -Amyloid clearance via alterations of MMP-9/TIMP-1

David Wink

Poster Session 2

Monday, January 23 • Ballroom 2 & 3

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

P22. Transcription factor Nrf2 modulates microglia/macrophage-mediated phagocytosis and contributes to hematoma resolution after intracerebral hemorrhage

Jaroslav Aronowski

P23. Repeated amphetamine causes long-lasting plasticity at prefrontal cortical terminals within the nucleus accumbens core

Nigel Bamford

P24. Grafting of neural stem cells to the hippocampus of young, irradiated mouse brains ameliorated behavior deficits

Klas Blomgren

P25. Intermittent availability of alcohol does not necessarily lead to elevated drinking in mice

John Crabbe

P26. ETrA antagonist administered at various time points after TBI indicates time-dependent improvement in cerebral blood flow as measured by arterial spin labeling-MRI

Justin Graves

P27. Dose-dependent effects of disulfiram on choices for cocaine over a monetary alternative in cocaine-dependent volunteers

Colin Haile

P28. HDAC6 regulates GR signaling in serotonin pathways with critical impact on stress resilience

Olivier Berton

P29. Exendin-4–induced glucagon-like peptide-1 (GLP-1) receptor activation reverses behavioral impairments of mild traumatic brain injury in rodents

Harold Holloway

P30. The spinal central pattern generator mediates anesthetic-induced immobility across vertebrate evolution

Steven Jinks

P31. Gene X early environment interactions determine prefrontal cortex DNA methylation status and drug-seeking in adult mice

Tod Kippin

P32. Endothelin A receptor antagonism in traumatic brain injury leads to improvement of both histopathologic and behavioral outcome

Anthony Kropinski

P33. Parkinson's disease biomarkers: Metabolomic analysis of CSF

Peter LeWitt

P34. Dopamine regulation of lateral habenula neuronal activity via blockade of tonic GABA-B receptor inhibition

Carl Lupica

- P35. Effects on neurobehavior of lead and manganese in rats developmentally-exposed: A gender-based comparison of individual and combined exposures
Timothy Maher
- P36. Mechanisms of gain-control in neural circuits revealed by nonlinear signal analysis with white noise photic stimulation
David Naylor
- P37. Molecular determinants of NMDA receptor allosteric potentiation
Kevin Ogden
- P38. Evaluation of quantitative proteomics for the analysis of human plasma in search for potential neurological biomarkers
Tulen Pekny
- P39. Synuclein promoter polymorphisms are associated with cognitive outcome after mild traumatic brain injury
C. Harker Rhodes
- P40. Cellular engraftment into the spinal cord of NUDE rat
Monica Siegenthaler
- P41. A melatonin receptors heteromer regulates the daily rhythm of visual processing in mouse
Gianluca Tosini
- P42. Novel apolipoprotein-E-mimetics improve behavior, reduce neuronal loss, and reduce pathology in CV-AD and CVND-AD mice
Michael Vitek
- P43. Nicotine and Varenicline activate nicotinic acetylcholine receptors on GABAergic neurons in hippocampus and medial septum/diagonal band
Ursula Winzer-Serhan

Poster Session 3

Tuesday, January 24 • Ballroom 2 & 3

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

P44. Partial monoamine loss induced by methamphetamine impairs Arc/Arg 3.1 mRNA expression in striatal efferent neurons

Melissa Barker-Haliski

P45. Seizure-induced mTOR hyperactivation modulates aberrant hippocampal dendritic structure and ion channel localization in epilepsy

Amy Brewster

P46. Cocaine experience dynamically alters DNA methylation at plasticity genes within the nucleus accumbens

Jeremy J. Day

P47. Nitric oxide synthase isoform expression and activity in methamphetamine-induced striatal toxicity

Danielle Friend

P48. mRNA-miRNA responses to depolarization in neuronal cells

Belinda Goldie

P49. Ammonia contributes to methamphetamine-induced neurotoxicity

Laura Halpin

P50. PKC phosphorylates GluA1 to increase AMPA receptor conductance

Meagan Jenkins

P51. The development of lead compounds for the next generation of antidepressants?

Claus Løland

P52. Opioid-sensitive GABA inputs from rostromedial tegmental nucleus synapse onto midbrain dopamine neurons

Aya Matsui

P53. TRPC1 and TRPC3 channels regulate intracellular calcium homeostasis and visual sensitivity in the mouse retina

Tunde Molnar

P54. Serial exposure to stress and methamphetamine results in persistent alterations in the structure and function of the blood brain barrier: Role of neuroinflammation

Nicole Northrop

P55. Subunit-selective allosteric inhibition of glycine binding to NMDA receptors

Kevin Ogden

P56. Mg²⁺-dependent modulation of cell–cell coupling and voltage gating in neuronal gap junction channels

Nicolas Palacios-Prado

P57. Simultaneous representation of goal information and hand kinematics in dorsal premotor cortex during reach planning and execution

Thomas Pearce

P58. D1 dopamine receptors in the nucleus accumbens are critical for enhanced amphetamine reward and nucleus accumbens deltafosb accumulation caused by sexual experience in male rats

Kyle Pitchers

P59. The mechanosensitive cation channel TRPV4 is a major regulator of calcium homeostasis in radial astroglia of the vertebrate retina

Daniel Ryskamp

P60. Abnormalities of FKBP5 and BAG1 within the glucocorticoid receptor stress signalling pathway in schizophrenia and bipolar disorder

Duncan Sinclair

P61. Latent inhibition is impaired by brain adenosine hypofunction: An adenosinergic link to schizophrenia-related attentional dysfunction

Philipp Singer

P62. Physiological normoxia enables reliable and efficient generation of neural precursor cells, motor neurons, and dopaminergic neurons from human embryonic stem cells

Sybil Stacpoole

P63. Prior trauma moderates amygdalar connectivity during “unseen” cues in cocaine-dependent patients

Jesse Suh

P64. Elevated low-frequency power across resting, sensory, and cognitive conditions in schizophrenia

Elyse Sullivan

Poster Session 4

Wednesday, January 25 • Ballroom 2 & 3

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

- P65. Dietary melatonin reverses age-related elevations in inflammatory genes and also reduces tumor size and number in aged mice

Stephen Bondy

- P66. Deciphering the role of myostatin in sarcopenia and neuromuscular degeneration in aging

Sonsoles De Lacalle

- P67. Vector-mediated delivery of clostridial C3 transferase to enhance spinal regeneration

David Fink

- P68. Naturally occurring neuronal apoptosis and caspase-3 activation in the brains of adult control rats and those with prolonged seizures

Denson Fujikawa

- P69. Effects of self-vocalization on human subcortical firing

Jeremy Greenlee

- P70. Neurofeedback: Panacea? Placebo? Parachute?

Eric Harris

- P71. Identifying novel LRRK2 substrates to elucidate the role of this kinase in Parkinson's disease pathophysiology

Warren Hirst

- P72. Anesthesia alters local field potential avalanches in rat visual cortex in vivo

Anthony Hudetz

- P73. Dopamine oxidation facilitates rotenone-dependent potentiation of NMDA currents in rat substantia nigra dopamine neurons

Steven Johnson

- P74. Molecular determinants for subtype-selective ion channel block of NMDA receptors by argiotoxin analogs

Anders Kristensen

- P75. Right hemisphere dominance of ERP responses to voice auditory feedback in singers with perfect pitch

Charles Larson

- P76. NGF precursor protein is elevated in CSF following acute spinal cord injury: Improving detection of therapeutic targets

Matthew Light

- P77. The genetic signatures of transposable elements (TE) in schizophrenia

Fabio Macciardi

- P78. Analysis of neurogenesis in the postembryonic hypothalamus of zebrafish

Adam McPherson

- P79. Analysis of dopamine D2 receptor mutants deficient in Arrestin3 binding using bioluminescence resonance energy transfer

Kim Neve

P80. Partial methamphetamine-induced striatal dopamine loss causes a change in circuitry mediating Arc-regulated response reversal learning

Elissa Pastuzyn

P81. Zebrafish: An in vivo model for CNS axonal regeneration after injury

Jeffery Plunkett

P82. Orbitofrontal cortex is necessary when behavior is based on inferred but not cached values

Geoffrey Schoenbaum

P83. Stereotypic perseverative instrumental behavior associated with methamphetamine-induced neurotoxicity in rats

Jong-Hyun Son

P84. Primary neuronal brainstem culture from adult zebrafish: Interactions with an inhibitory chondroitin sulfate proteoglycan-rich environment

Alexis Tapanes-Castillo

P85. Mono- or polytherapy in the treatment of acute seizures and status epilepticus

Claude Wasterlain

P86. Effect of mild traumatic brain injury (mTBI) on the hypothalamic-pituitary-adrenal axis feedback

Tao (John) Wu

Session Abstracts

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

1. Controlling the brain with light: An optogenetic approach to study the neural circuit basis of behavior

Chair: Donna Calu

Presenters: Kay Tye, Garret Stuber, Melissa Warden, Donna Calu

Neuroscientists have long sought a method to control neural activity in the brain in a temporally precise and cell-specific fashion. The development of optogenetics, or the use of genetically-targetable light-sensitive proteins in neural systems, allows neuroscientists to manipulate (activate or silence) activity in targeted neuronal populations on a physiologically-relevant (i.e., millisecond) timescale. The precise control achieved with an optogenetic approach allows investigators to demonstrate a causal role for specific neuronal populations or neural networks in animal behavior, brain disorders, and therapeutic avenues. This panel will describe recent advances in the implementation of optogenetic tools for the systematic investigation of neural circuits or circuit elements in the control of physiological and motivational behaviors. First, Kay Tye will demonstrate how cell-specific targeting of light-sensitive proteins to and selective optical manipulation of ventral tegmental area (VTA) dopamine neurons (using Th:Cre transgenic rodents) reveals a role for this neuronal population in motivational (escape-related behavior) or hedonic behavioral symptoms related to depression. Next, Garret Stuber will present data demonstrating the effects of optically stimulating VTA GABA synapses, both locally within VTA and distally projecting to VTA, on reward seeking behaviors. Then, Melissa Warden will provide optogenetic evidence for the involvement of the medial prefrontal cortex projection to the dorsal raphe nucleus in antidepressant-like behavioral responses. Finally, Donna Calu will describe the effect of optically inhibiting dorsal medial prefrontal cortex on reinstatement of palatable food seeking.

2. Pharmacology gone wild in the world of addiction neurobiology

Chair: Christopher Evans

Presenters: Arynah Pradhan, Mark von Zastrow, Ken Mackie, Charles Chavkin

The observation that different agonists can act at the same receptor to trigger distinct signaling, trafficking and desensitization profiles has catalyzed therapeutic strategies to develop new ligands with selected behavioral profiles at the same old receptor targets. Furthermore, we know that “antagonists” are not all created equally; some are inverse agonists, some merely block receptor occupation by agonists, and some trigger signaling cascades that can block receptor activation for months. This panel will reveal new insights into ligand-directed signaling at opioid and cannabinoid receptors. Following a short introduction by Chris Evans (UCLA), Arynah Pradhan (UCLA) will present data on the role of beta-arrestins in directing ligand-specific delta opioid receptor desensitization in vivo. Mark von Zastrow (UCSF) will describe new mechanistic studies to elucidate the underpinnings of ligand bias using advances in biophysical and biochemical analytical methods, developed over the last several years. Ken Mackie (Indiana University) will then present recent results from his laboratory demonstrating that CB2 agonists exhibit striking functional selectivity, which may explain the differences in behavioral and clinical responses to different classes of CB2 agonists. Finally, Charles Chavkin (University of Washington) will venture into the new territory of collateral agonists at the kappa opioid receptor that signal via a Jnk-signaling pathway to block kappa receptor activation for months. Jnk-signaling will also be implicated in agonist-biased mechanisms of tolerance at mu-opioid receptors. Together, the presentations will reveal a new appreciation of diversity in ligand interactions via G-protein coupled receptors and highlight future targets for drug development.

3. Neurodevelopment, neurodegeneration, and cognition in psychiatric disorders across the lifespan

Chair: Jeremy Koppel

Presenters: Anil Malhotra, Katherine Burdick, Jeremy Koppel, Thomas Hyde

Neurocognitive dysfunction is common to multiple neuropsychiatric disorders. Cognitive deficits may be noted premorbidly and reflect neurodevelopmental processes, or they can be acquired as a result of a degenerative process (cognitive decline). This panel will discuss cognition at the level of human

data, focusing on diseases across the lifespan including schizophrenia, bipolar disorder, and Alzheimer's disease. In addition, we will touch upon psychiatric brain banking and the approaches used for both developmental abnormalities and neurodegenerative processes. Anil Malhotra (The Feinstein Institute for Medical Research) will present evidence that schizophrenia can largely be understood as a disorder of neurodevelopment with a strong genetic contribution. Next, Katherine Burdick (Mount Sinai School of Medicine) will present data to suggest that bipolar disorder is a somewhat unique example of a cognitive disorder with evidence for both a neurodevelopmental deficit and a notable component of cognitive decline. Jeremy Koppel (The Feinstein Institute for Medical Research) will present evidence that psychosis accelerates cognitive decline and mortality in AD, suggesting disease subcategorization (AD+P), together with cognitive and imaging data from two new studies that suggest a frontal localization of this disease. Finally, Thomas Hyde (NIMH) will present data of the profile of gene expression in the prefrontal cortex as it relates to normal human development and neuropsychiatric disease. He will present evidence that polymorphisms in genes associated with schizophrenia may primarily exert their deleterious effects during early brain development.

Panel • Sunday, 4:30–6:30 PM • Maybird

4. Calcium channel regulation and presynaptic plasticity

Chair: William Catterall

Presenters: William Catterall, Thomas Sudhof, Karina Leal, Diane Lipscombe

Short-term synaptic plasticity was first described in classic work by Katz and Miledi in the 1960s, but the molecular mechanisms that regulate expression and function of presynaptic calcium channels and underlie this form of synaptic regulation are only now being defined. Localization of calcium channels in presynaptic terminals is dependent on interactions with the SNARE complex that mediates neurotransmitter release, including interactions with presynaptic regulators of SNARE proteins, as well as SNARE proteins themselves. Short-term synaptic facilitation and depression, on the time scale of milliseconds to seconds, is mediated in part by calcium-dependent regulation of presynaptic calcium channels by calcium-sensor proteins. The function of presynaptic calcium channels is also regulated by neurotransmitters acting through G protein-coupled receptors, which provide negative feedback control of transmitter release. In this panel, Catterall will present an overview of calcium channel structure and regulation and their implications for presynaptic function and plasticity. Sudhof will present his work showing that the SNARE-interacting protein RIM is required for normal recruitment of presynaptic calcium channels and for regulation of their function. Leal will present her research showing

that calmodulin-like calcium-sensor proteins regulate the function of presynaptic calcium channels and thereby provide a bidirectional switch controlling synaptic facilitation and depression. Lipscombe will complete the panel with a presentation of her research showing that alternative splicing of a presynaptic calcium channel controls the response of the sensory primary-afferent synapse to regulation by opiate peptides and analgesics. The panel will finish with a discussion of the relative roles of these different signaling mechanisms in determining basal calcium channel function at the synapse and its up- and down-regulation in response to neurotransmitters and synaptic activity.

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

5. Effects of insulin in the mesolimbic dopamine system

Chair: Stephanie Borgland

Presenters: Stephanie Borgland, Aurelio Galli, Margaret Rice, Tommy Pattij

Obesity rates have drastically increased over the last few decades. While much research has focused on the homeostatic regulation of metabolism, this does not work very well in an environment where little effort is necessary to procure palatable, highly caloric food. Dopamine neurons of the mesolimbic circuit, including the ventral tegmental area (VTA) and nucleus accumbens (NAc), mediate reward-seeking behaviors, and plasticity of this system may override the homeostatic system's control of food intake. So far, little is known about how circulating peptides, such as insulin, that signal the cessation of eating, modulate the activity of dopamine neurons. This panel will explore how insulin action in the mesolimbic system can modulate dopamine output and related behavior. Stephanie Borgland (UBC) will provide evidence that insulin suppresses somatodendritic dopamine concentration by increasing dopamine reuptake in VTA brain slices. Aurelio Galli (Vanderbilt) will present work showing that consumption of fat-rich food impairs striatal activation of the insulin-activated signaling kinase, Akt. High fat consumption-induced Akt impairment, in turn, reduces dopamine transporter cell surface expression and function, thereby decreasing dopamine homeostasis and amphetamine-induced dopamine efflux. Margaret Rice (NYU) will present recent findings from her group showing that nM levels of insulin increase evoked dopamine release in the dorsal striatum and in the NAc shell and core. The effect is mediated by insulin receptors but is independent of any influence of insulin on the dopamine transporter. Lastly, Tommy Pattij (VUMC) will show neurochemical data indicating that insulin reduces dopamine release in the NAc and potentiates the effects of cocaine on release of this neurotransmitter in this brain region. Moreover, he will present behavioral data indicating that insulin modulates impulsivity and cocaine's effects on impulsive behavior and not locomotor behavior.

6. Can we really figure out repair in the adult by studying development?

Chair: Wendy Macklin

Presenters: Jonah Chan, Steven Fancy, Teresa Wood, Sybil Stacpoole

Is there a difference in myelination that occurs initially during development relative to remyelination in the adult following injury? Understanding the developmental regulation of oligodendrocyte lineage specification and the transcriptional and translational regulation of myelination has clear relevance to developmental disorders. The expectation has been that understanding how myelination occurs during development will also provide direct insight into remyelination in such diseases as multiple sclerosis (MS), which is a demyelinating disease that attacks the adult CNS. Clearly, repair through remyelination is essential for recovery in MS and other demyelinating diseases, and investigators are using clues from development to investigate repair in the adult CNS. We will address this question in talks discussing new data on the regulation of oligodendrocyte production, differentiation, and myelination during development, relative to repair. Dr. Jonah Chan (University of California, San Francisco, UCSF) will discuss how identifying inhibitory mechanisms important for the spatiotemporal regulation of myelination during development may also relate to repair and remyelination. Dr. Steven Fancy (UCSF) will discuss the transcriptional control of oligodendrocyte differentiation, particularly focusing on the role of the wnt pathway in remyelination. Dr. Terri Wood (University of Medicine and Dentistry of New Jersey) will discuss the signaling pathways regulating myelination, with a focus on the role of mTOR signaling in the regulation of oligodendrocyte development and during recovery from lysolecithin-induced demyelination in the adult. Dr. Sybil Stacpoole (Cambridge University) will discuss the application of developmental pathways to the generation of human oligodendrocytes from embryonic stem cells and how such oligodendrocyte lineage cells can be used to investigate the effects of potential remyelinating agents.

7. Are all addictions the same? A traditional symposium

Chair: John Mendelson

Presenters: John Mendelson, Jacqueline McGinty, Ghazaleh Sadri-Vakili

One of the underlying assumptions in addiction biology is that all addictive disorders stem from disordered pathology in reward circuitry. In this session, we will discuss some of the evidence for and against this assumption. To achieve a broader, modern understanding of this broad topic, we will re-introduce the ancient method of the symposia. From *sym* (together) and *poiesis* (drinking) originated a lively and fun method to advance learning and knowledge. In ancient Greece, the drinking, talking, and learning were supervised by *Symposiarchs*. The *Symposiarchs* for this session are John Mendelson and Jacqueline McGinty. Mendelson is a clinical researcher and clinician interested in mechanisms of addictive drug action. Under laboratory conditions, he has administered methamphetamine, MDMA, cocaine, various opiates, and alcohol to drug abusers and addicts. He will support the argument that the extant clinical evidence suggests a heterogeneous range of diseases that do not all act through reward dysfunction. McGinty is a basic scientist who studies gene/protein expression in animal models of addiction. Her recent work focuses on the role of brain-derived neurotrophic factor on cocaine-seeking. She will lead a debate about the most valid animal models of addiction. Symposia were also used to introduce new faces to society, so we have asked Ghazaleh Sadri-Vakili to add her voice to a discussion of whether epigenetic markers for addiction are inheritable. A polemical moment: Does anyone else wonder how our system of PowerPoint presentations has shaped our science? If so—join us for an alternative. We have asked for an 8:30 slot and plan a participatory evening. We encourage all who want to join in to sign up early. We will continue the tradition of drinking together but with a few enhancements to make participation more likely. To speak, participants must raise their glasses and keep them raised while making comments—arms will tire when ideas falter.

8. Neuroprotection, rehabilitation, and regeneration of the alcohol-exposed CNS

Chair: Jennifer Thomas

Presenters: Jennifer Thomas, Alexandre Medina, Kim Nixon

Alcohol exposure during any period of development can damage the CNS. Elucidation of how alcohol affects life span plasticity, as well as factors that can protect against alcohol's toxic effects and/or enhance neuronal plasticity following an alcohol insult, is important for the development of strategies to treat individuals with fetal alcohol spectrum disorders, as well as adolescents and adults with alcohol-use disorders. This symposium will explore pharmacological, nutritional, and behavioral factors that protect the CNS or influence recovery from alcohol-induced CNS injury. Using a rodent model, Jennifer Thomas will demonstrate that administration of choline, an essential nutrient, can reduce behavioral deficits associated with developmental alcohol exposure even when administered long after the alcohol exposure. Choline supplementation may attenuate alcohol's teratogenic effects by altering cholinergic functioning and by leading to long-lasting epigenetic changes. Alexandre Medina will present findings obtained with a combination of imaging and electrophysiological techniques, showing that pharmacological phosphodiesterase inhibition can improve cortical plasticity in different species of animals exposed to alcohol during development. Finally, Kim Nixon will illustrate that environmental and pharmacological factors that influence hippocampal neurogenesis can reduce the consequences of alcohol exposure during adolescence and adulthood.

9. Cannabinoids and schizophrenia: What's pot got to do with it?

Chair: Joseph Cheer

Presenters: Roger Cachepe, Kuei Tseng, Deepak Dsouza

Clinical and experimental data suggest that plant-derived as well as endocannabinoids are implicated in schizophrenia. Indeed, the brain levels of the endocannabinoid anandamide are elevated in the spinal fluid of schizophrenic patients, and postmortem studies have shown that the expression of cannabinoid receptors (CB1) is greatly increased in several brain areas related to cognitive processes, such as reinforcement processing. Because negative symptoms of schizophrenia include lack of motivation and antagonism of CB1 receptors decreases motivation for food, Roger Cachepe hypothesized that increasing levels of endocannabinoids could enhance motivation in the DISC1 mouse

model of schizophrenia. He finds that raising 2AG levels increases motivation in 90-day but not in 150-day-old mice. This is accompanied by an increase in gamma power recorded from accumbal oscillations in 90-day-old mice only, suggesting that critical adaptations of endocannabinoid signaling occur in older DISC1 mice. Conversely, marijuana use during adolescence is associated with an increased risk for schizophrenia. Kuei Tseng finds that activation of CB1 receptors during adolescence is sufficient to disrupt the normal developmental maturation of fast-spiking interneuron function in the prefrontal cortex. This can in turn foster a disinhibited prefrontal cortex, which may contribute to an increased risk for psychiatric disorders. Finally, Deepak Dsouza will discuss findings from a clinical sample composed of healthy individuals, light users of cannabis, and individuals with schizophrenia. He measured the effects of THC (the main psychoactive component in marijuana) on schizophrenia-relevant outcomes and finds positive and negative symptoms, perceptual alterations, and deficits in verbal memory, attention, and working memory deficits, as well as psychophysiological abnormalities in healthy individuals. Of note, THC exacerbates symptoms in individuals with schizophrenia.

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

10. NMDA receptor signaling: New turns and twists

Chair: R. Suzanne Zukin

Presenters: R. Suzanne Zukin, Stephen F. Traynelis, Mark Dell'Acqua

This panel will highlight recent developments in the area of N-methyl-D-aspartate receptors (NMDARs) in synaptic function and plasticity. NMDARs are glutamate-gated ion channels that play a pivotal role in synaptogenesis, neural circuitry, and higher cognitive functions such as learning and memory. The precise subunit composition determines NMDAR functional properties. A hallmark feature of NMDARs in forebrain is a developmental switch from primarily NR2B- to NR2A-containing during postnatal development. Although the switch in phenotype has been an area of intense interest for two decades, the link between experience and the switch are unclear. Zukin will present exciting new findings that the gene-silencing transcription factor REST acts via epigenetic remodeling to drive the developmental switch in synaptic NMDA receptors. Traynelis will present new data that NMDARs containing the GluN2D subunit are expressed in the thalamus, where they influence tonic firing properties of subthalamic neurons. These data reveal a previously unappreciated function for GluN2D-containing receptors in synaptic function and plasticity. Dell'Acqua will present exciting new findings that NMDA receptor-dependent synaptic plasticity is regulated by AKAP-anchored calcineurin. He will provide evidence that AKAP150/DPIX knockin mice, which express a mutated form of AKAP-

150 lacking the calcineurin anchoring site, exhibit deficits in AMPAR phosphorylation and trafficking as well as NMDAR-dependent LTD and LTP at CA1 synapses.

Panel • Sunday, 8:30-10:00 PM • Superior A

11. New ideas on chronic pain

Chair: Juan Carlos Marvizon

Presenters: Juan Carlos Marvizon, Ann Gregus, Lucy Vulchanova, Bradley Taylor

Chronic pain disorders affect a large segment of the population, have a large impact on work productivity and quality of life, and often lack effective treatments. Recent discoveries have increased our knowledge of the many adverse effects of common treatments against pain, namely morphine and similar opiates. Therefore, it is imperative to find new molecular targets for the development of new pain medication. This panel will explore some of these new possibilities. Dr. Juan Carlos Marvizon (UCLA) will chair the panel. He will present new discoveries on the mechanisms that regulate synaptic transmission between sensory afferents and spinal cord neurons, which is crucial in controlling the intensity of pain. He will discuss the role of tyrosine kinases in modulating presynaptic NMDA receptors and in mediating the interaction of mu-opioid, GABAB, and alpha-2 adrenergic receptors with voltage-gated calcium channels, and how these systems change during chronic pain.

Dr. Ann Gregus (UCSD) will outline the roles of various lipid mediators in pain processing, in particular eicosanoids (derived from COX, LOX, or CYP) and endocannabinoids. She will focus on how 12-LOX metabolites modulate inflammatory hyperalgesia. Dr. Lucy Vulchanova (University of Minnesota) will present her work on the neurosecretory protein VGF, which is a neuropeptide precursor related to the chromogranins. It is rapidly and robustly upregulated in sensory neurons after nerve injury. She is studying the signaling mechanisms of VGF-derived peptides and their contribution to the development and maintenance of neuropathic pain. Dr. Bradley Taylor (University of Kentucky) will show that spinal opioid and NPY receptors exert a tonic, long-lasting inhibitory control of pain transmission in the spinal cord, impeding the transition from acute to chronic pain. They may also help in the recovery from the hyperalgesia associated with inflammation or nerve injury.

12. Glial cells: An overlooked regulator of neural activity

Chair: David Baker

Presenters: Cagla Eroglu, Dorothy Schafer, David Stellwagen, David Baker

Billions of dollars has been spent to fund over a million studies devoted to understanding the neuron, a cell held in such prominence that it provided the field its name. In comparison, there have been fewer than 40K publications examining the role of astrocytes, a cell type as numerous as neurons in the human brain. Unfortunately, our knowledge of the neuron has yet to result in the development of effective, well-tolerated treatment for most, if not all, pathologies of the brain. Thus, one has to consider the possibility that this is a consequence, at least in part, of our historical approach of a near-exclusive focus on the neuron. Recently, it is becoming clear that the contribution of glial cells to brain functioning goes well beyond the role typically envisioned for these cells. The goal of the panel is to demonstrate the diverse ways in which glial cells are emerging as key determinants of brain functioning in normal and pathological states. Specifically, Cagla Eroglu (Duke University) will present her recent findings that astrocytes are key regulators of synaptogenesis. Dorothy Schafer (Harvard Medical) will demonstrate a new role for microglia during synaptic pruning and provides evidence that neural activity can directly influence interactions between microglia and synaptic elements. Next, David Stellwagen (McGill University) will discuss his data implicating astrocytes in regulating synaptic plasticity in the striatum through the trafficking of glutamate receptors. David Baker (Marquette University) will close by presenting data implicating glutamate release from astrocytes via cystine-glutamate exchange in diseases of the brain, including addiction and schizophrenia.

13. Impaired neural plasticity and NMDA receptor hypofunction in schizophrenia: A challenge for more effective treatment

Chair: Joseph Coyle

Presenters: Joseph Coyle, Robert Schwarcz, Z. Jeff Daskalakis, Don Goff

Pharmacologic, postmortem, and genetic studies indicate that hypofunction of NMDA receptors plays a critical role in the pathophysiology of schizophrenia. Joseph Coyle (McLean Hospital/Harvard Medical School) will review this evidence and show from mouse genetic models that reduced NMDA receptor function reproduces the cortical atrophy, dendritic dysplasia, reduced spine

density, and altered gene expression characteristic of schizophrenia. Robert Schwarcz (University of Maryland) will review recent findings on the role of kynurenic acid (KA), an endogenous antagonist at NMDA receptor and alpha-7 nicotinic receptor, in schizophrenia. KA levels are elevated in brain and CSF in schizophrenia. He recently has found that the expression of a critical enzyme regulating KA levels, kynurenine-3-monooxygenase (KMO), is reduced in the brain in schizophrenia. Jeff Daskalakis (Centre for Addiction and Mental Health, Toronto) has exploited transcranial magnetic stimulation to evaluate neural plasticity in patients with schizophrenia. Using a motor learning paradigm, he has demonstrated reduced neural plasticity in unmediated schizophrenic subjects, consistent with impaired NMDA receptor function. Don Goff (Massachusetts General Hospital/Harvard Medical School) pioneered the use of D-cycloserine (DCS), a partial agonist at the glycine modulatory site of the NMDA receptor, to enhance NMDA receptor function. He will review the results of a placebo-controlled clinical trial demonstrating that DCS significantly improves outcomes when coupled with cognitive remediation in schizophrenia. Thus, the panel will provide a compelling translational presentation on the central role of NMDA receptor hypofunction in the pathophysiology of schizophrenia and strategies to overcome this deficit to improve treatment.

Panel • Monday, 7:30–9:30 am • Maggie

14. Challenges and opportunities in treatment discovery for nicotine dependence: An integrated perspective

Chair: Athina Markou

Presenters: Phil Skolnick, Athina Markou, Paul Kenny, Caryn Lerman

This panel aims to bring together scientists from diverse disciplines, backgrounds, and perspectives to explore how advancements can be made in discovering and developing new treatment approaches for tobacco dependence in the context of discussing the economics of drug discovery efforts, and presenting drug discovery efforts in this arena by three academic laboratories. Nicotine is the major psychoactive ingredient in tobacco that contributes to tobacco dependence, and thus the harmful tobacco-smoking habit. Thus, preclinical work is focused on identifying pharmacological treatments to treat the various aspects of nicotine dependence. Phil Skolnick will discuss the economics of drug discovery for this indication. He will also identify barriers in making progress in discovering and bringing to the market treatments for nicotine dependence. Athina Markou will discuss how by using animal models of aspects of nicotine dependence novel pharmacological targets can be identified and validated for treating nicotine dependence. She will specifically discuss

metabotropic glutamate 2/3 receptors as targets for the development of new medications to assist people to quit smoking. Paul Kenny will discuss the involvement of orexin-1 (hypocretin-1) receptors in nicotine dependence, and highlight efforts to develop novel small molecule orexin-1 receptors antagonists as potential therapeutics for nicotine dependence. Finally, Caryn Lerman will discuss novel human laboratory research methods to identify new smoking cessation medications, particularly those targeting cognition. This panel will use concrete examples from various disciplines to discuss principles of drug discovery and development of treatments for smoking cessation. Challenges and opportunities will be discussed as means of advancing the field, and identifying integrative and translational approaches to the treatment of nicotine dependence.

Panel • Monday, 7:30–9:30 AM • Wasatch

15. Modulation of dopamine neuron activity by afferents: Implications in reward

Chair: Kathy Toreson

Presenters: Kathy Toreson, Dennis Sparta, Carlos Paladini, Francois Georges

Dopamine is important for a plethora of behavioral and cognitive tasks, including voluntary movement, reward prediction error, attention, and working memory. Thus, an appropriate level of dopamine cell activity is essential for normal execution of such tasks. A proper balance between the excitatory and inhibitory drive onto these dopaminergic cells is crucial for appropriate dopamine neuron excitability. Importantly, natural stimuli as well as drugs of abuse are strong modulators of dopamine cell activity. This panel will explore several sources of inhibitory and excitatory drive onto dopaminergic neurons, and discuss how the balance of these inputs is altered by drugs of abuse. Kathy Toreson (University of Maryland at Baltimore) will present electrophysiological data on the influence of the orbitofrontal cortex (OFC) on histochemically identified dopaminergic neurons of the ventral tegmental area (VTA). Dennis Sparta (University of North Carolina at Chapel Hill) will present data on the projection from the bed nucleus of the stria terminalis (BNST) to the VTA, and how this pathway is affected by acute and repeated stressors. Carlos Paladini (University of Texas at San Antonio) will present data using ChR2 to investigate the integration of excitatory and inhibitory inputs on dopamine neurons. Finally, Francois Georges (University of Bordeaux) will discuss how GABAergic and glutamatergic terminals innervate and regulate the activity states of dopamine neurons and how drugs of abuse modify dopamine neurons physiology and thereby lead to addictive behavior.

16. Metabotropic glutamate receptor 4 (mGlu4) as a novel target for CNS drugs: From chemistry to behavior

Chair: Andrzej Pilc

Presenters: Francine Acher, Dario Doller, Colleen Niswender, Andrzej Pilc

Glutamate is the major excitatory neurotransmitter in the brain. While the ligands acting on ionotropic receptors exert a number of profound adverse effects in humans, the ligands of modulatory metabotropic (mGlu) receptors may become safer drugs. mGlu receptors are divided into three groups: group I, group II, and group III receptors. Concerning the group I/II mGlu receptors, a number of preclinical and some clinical data show their efficacy in various CNS diseases; the group III mGlu receptors have historically been less investigated. The group III receptors are divided into mGlu4, mGlu6, mGlu7, and mGlu8 receptors. New roles for mGlu4 in disease states, such as schizophrenia, anxiety, epilepsy, neurodegenerative disease (including Parkinson's Disease [PD]), suggest that compounds that manipulate mGlu4 function may serve as desirable therapeutics in a number of disease areas. The panel will discuss the discovery and central effects of mGlu4 receptor ligands. Francine Acher (CNRS, France) will present the discovery of a hit by means of a virtual high throughput screening of mGlu4 receptor binding domain and its optimization into LSP1-2111 and LSP4-2022 that display subtype 4 preference or selectivity among the group III receptors. Dario Doller (Lundbeck Research) will talk about the design and therapeutic potential of mGlu4 receptor positive allosteric modulators (PAMs). The issues being faced in the discovery of mGlu4 PAMs will be discussed, as well as new knowledge generated using a number of newly developed tool compounds. Colleen Niswender (Vanderbilt University) will provide an overview of the mGlu4 PAM program at Vanderbilt, suggesting that mGlu4 represents a novel target for symptomatic and disease-modifying treatment of PD. Andrzej Pilc (PAS, Poland) will present the data showing that the novel orthosteric agonists of group III mGlu receptors, as well as positive allosteric modulators of mGlu4 receptors, display anxiolytic-like activity in animal tests.

17. For they don't know what they are doing: Enduring effects of early-life stimulant exposure

Chair: Heinz Steiner

Presenters: Barry Kosofsky, Pradeep Bhide, Heinz Steiner, Carlos Bolaños

Psychostimulant abuse during brain development is thought to produce neuroadaptations that increase liability for drug addiction and other mental disorders later in life. Among the most affected brain systems are corticostriatal circuits. Drug-induced neuronal changes in these circuits are implicated in abnormal reward processes and mood regulation, as well as aberrant habit formation and compulsive behaviors. The effects of illicit stimulants such as cocaine (a dopamine/serotonin reuptake inhibitor) in modifying these circuits are well established. Intriguingly, recent studies indicate that methylphenidate (Ritalin; dopamine reuptake blocker), a stimulant used to treat ADHD and abused as a cognitive enhancer, can have similar molecular effects. Moreover, some of these effects are potentiated by addition of selective serotonin reuptake inhibitors (SSRIs), drugs increasingly prescribed in pediatric populations. This panel will discuss recent advances in our understanding of the molecular effects of early stimulant exposure and their lasting behavioral consequences. First, Barry Kosofsky (Weill-Cornell Medical College) will show that prenatal cocaine exposure results in impaired fear extinction in adult mice, due to blunted BDNF signaling in the prefrontal cortex. Pradeep Bhide (Massachusetts General Hospital) will discuss how prenatal cocaine exposure alters development of GABA circuits and BDNF signaling in the frontal cortex, effects that may be heritable via epigenetic mechanisms. Heinz Steiner (RFUMS/Chicago Medical School) will summarize cocaine-like gene regulation by methylphenidate in the adolescent striatum and will show how such effects are potentiated by co-exposure to SSRIs. Finally, Carlos Bolaños (Florida State University) will show how methylphenidate+SSRI treatment in juveniles promotes deficits in reward/mood regulation in adults, and that disruptions in ERK/BDNF signaling in midbrain dopamine neurons contribute to these behavioral abnormalities.

18. Glia: A nemesis in opioid use

Chair: Cathy Cahill

Presenters: Tuan Trang, Kurt Hauser, Anna Taylor, Daniela Salvemini

Over the past decade, glia have emerged as novel and unexpected cellular targets of opioid drugs. Activity of glia is increasingly recognized as being critically involved the development and maintenance of opioid analgesic tolerance

and exacerbating diseases such as HIV infection. There is also recognition that targeting glial is a valid strategy for managing various diseases including neurodegenerative diseases, HIV infection, and chronic neuropathic pain. Considering that opioids remain the most common therapeutic for treating pain, there is a dire need to assess whether opioid treatment may exacerbate disease pathology. This panel will discuss mechanisms underlying opioid-induced glial activation and the functional implications such activation has on various diseases. Following a short introduction by Dr. Cahill, Dr. Tuan Trang (Hosp Sick Kids) will present new evidence that spinal microglia are involved in morphine-induced hyperalgesia, but not opioid tolerance, and that the P2X4R-BDNF-KCC2 signaling pathway previously implicated in neuropathic pain is recruited with chronic opioid treatment. Dr. Kurt Hauser (VCU) will present evidence that opioids exacerbate the pathogenesis of human immunodeficiency virus-1 (HIV-1) through direct actions on glia. Dr. Anna Taylor (UCLA) will present elegant data implicating glial cell activation in altered reward circuitry in chronic pain conditions. Her data suggest that the circuitry for opioid reward is different in animals depending on whether they are in chronic pain and that glial inhibitors can block opioid reinforcement effects in chronic pain. Wrapping the session up, Dr. Daniela Salvemini (St Louis Univ) will discuss novel therapeutic strategies targeting S1P to attenuate opiate-induced hyperalgesia and antinociceptive tolerance. Her work suggests that anti-S1P therapies are effective at least in part through modulation of glia cell reactivity and glia-to-neurons interactions.

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

19. Imaging the human dopamine system: An updated view of the inverted U

Chair: Elizabeth Tunbridge

Presenters: Elizabeth Tunbridge, Oliver Howes, Daniel Weinberger, Paul Phillips

Dopamine is a critical mediator of cognition and psychosis and is implicated in numerous psychiatric disorders. The most notable of these is schizophrenia, a disorder in which patients suffer from both psychosis and cognitive deficits. Excessive dopaminergic transmission in the striatum is thought to underlie psychosis, whilst dopamine in the prefrontal cortex modulates cognitive function; performance is impaired by both excessive and insufficient dopamine and thus there is an inverted-U relationship between prefrontal dopamine and cognitive function. This panel will review approaches to imaging dopamine function in the human brain and how these technologies may shed light on our understanding of schizophrenia and other neuropsychiatric disorders. Dr. Liz Tunbridge (University of Oxford) will describe the results of her recent study

examining the impact of altered activity of the dopamine catabolic enzyme catechol-O-methyltransferase (COMT) on human behaviour and neural activity measured using magnetoencephalography. Dr. Oliver Howes (Kings College London and Imperial College) will discuss the relationship of striatal dopamine synthesis capacity (determined using PET) and brain activation (fMRI) to cognition and transition to psychosis in an at-risk group. Dr. Daniel Weinberger (Lieber Institute for Brain Development) will demonstrate how his group has used fMRI to investigate epistatic interactions between functional variations in dopamine signalling genes and brain activation. Finally, Dr. Paul Phillips (University of Washington) will describe recent technical developments that allow the direct real-time measurement of dopamine release in the human brain.

Panel • Monday, 4:30–6:30 PM • Magpie

20. Stress, drugs, and alcohol: The adolescent brain on a poorly groomed slope

Chair: Josh Gulley

Presenters: Cheryl McCormick, Frances Leslie, Josh Gulley, Christine Konradi

As individuals age from adolescence into adulthood, the brain undergoes significant changes in structure and function that may contribute to age-dependent differences in behavior. Research in both humans and laboratory animals has suggested that this normal developmental process may be perturbed by exposure to stress and drugs of abuse. Moreover, the effects of these early life experiences may be long lasting and have adverse consequences on behavior that last well into adulthood. Thus, it is important to determine if the mechanisms of experience-induced plasticity differ in adolescents compared to adults. In this panel, we will discuss age-dependent differences in the effects of stress and drug exposure, with an overall goal of identifying candidate mechanisms for enhanced vulnerability in adolescents. Cheryl McCormick (Brock University) will discuss the effects of social stress in adolescence on reward systems in adulthood as indicated by changes in behavioral responses to psychostimulants, sucrose intake, and sexual behaviour in a rat model. Frances Leslie (University of California, Irvine) will discuss the influence of nicotine on the development of dopamine and serotonin systems and related behaviors in adolescent rat. Josh Gulley (University of Illinois, Urbana-Champaign) will talk about his work showing a role for drug-induced changes in medial prefrontal cortex function in age of exposure-dependent effects of amphetamine and alcohol. Lastly, Christine Konradi (Vanderbilt University) will discuss the long-lasting consequences of binge-cocaine exposure during adolescence. Using a rat experimental model, behavioral abnormalities in adulthood and their potential molecular

underpinnings will be addressed. The data presented by the panel demonstrate the power of environmental factors to shape the adolescent brain and the dangers they present as they disrupt the normal developmental trajectory.

Panel • Monday, 4:30–6:30 PM • Wasatch

21. Genome sequencing of psychiatric disorders: An avalanche of new data

Chair: John Kelsoe

Presenters: John Kelsoe, James Knowles, Gonzalo Laje, Anil Malhotra

The recent development of very high throughput and inexpensive sequencing technologies is making possible a new era in gene mapping studies for neuro-psychiatric disorders. Genomewide association studies over the last several years have explored the role of common variants in psychiatric disorders by interrogating 1–2 million single nucleotide polymorphisms (SNPs). Though these studies have identified several new predisposing genes, these discoveries still explain only a very small portion of the total genetic variance. This suggests that common variants may be of limited importance in psychiatric illness, and instead genes predisposing to illness carry numerous rare variants each of which may have a large effect on risk. Only sequencing studies have the resolution to identify such variants and identify genes based on the excess load of functional mutation that they carry in psychiatrically ill individuals. In this panel, some of the earliest work on whole genome and exome sequencing will be described, and the potential of this technology discussed. John Kelsoe (University of California, San Diego) will describe the whole genome sequencing of a proband in a family co-segregating for both bipolar disorder and medullary cystic kidney disease, and how it led to the identification of a deleterious missense mutation in the *NTRK1* gene that may cause both disorders. Jim Knowles (University of Southern California) will describe whole genome sequencing studies of families with schizophrenia in an Azorean population isolate. Gonzalo Laje (National Institute of Mental Health) will present results from exome sequencing of antidepressant treatment outcome in major depression. Lastly, early results of exome sequencing in families with schizophrenia will be presented by Anil Malhotra (Zucker Hillside Hospital).

22. PICK1 is not picky: From synaptic plasticity to neuroendocrine secretion and male infertility

Chair: Ulrik Gether

Presenters: Kenneth L. Madsen, Richard L. Huganir, Jun Xia, Ulrik Gether

Protein interacting with C kinase 1 (PICK1) is a synaptic scaffolding protein characterized by an N-terminal PSD-95/Discs-large/ZO-1 homology (PDZ) domain. The PDZ domain binds both the C-terminus of protein kinase Ca (PKC α) and the C-termini of several receptors and transporters, e.g., the GluA2/3 subunits of AMPA receptors (AMPA receptors). PICK1 is unique among PDZ domain proteins by also containing a BAR (Bin/amphiphysin/Rvs) domain, a crescent-shaped dimeric α -helical module that both can sense and impose membrane curvature. PICK1 is mostly known for its role in LTD by regulating AMPAR trafficking and AMPAR subunit composition. More recently, PICK1 has been implicated in LTP and synaptic scaling as well as having been suggested as a new target for treatment of stroke and neuropathic pain. Furthermore, novel data suggest that PICK1 controls biogenesis of secretory vesicles, and that PICK1 deficiency leads to impairment of neuroendocrine secretion and male infertility. This panel will present the most recent insights into the manifold physiological roles of PICK1 and the molecular mechanisms underlying this remarkable functional diversity. Kenneth Madsen (Univ. of Copenhagen) will introduce PICK1 and describe molecular mechanisms underlying the lipid binding and membrane sculpting capacity of the PICK1 BAR domain and how this is regulated by phosphorylation. Rick Huganir (Johns Hopkins Univ.) will describe the critical role of the PICK1 protein during fear conditioning and fear-induced synaptic potentiation in the amygdala. Jun Xia (Hong Kong Univ. of Sci. & Tech.) will explain how PICK1 forms tight heterodimeric complexes with ICA69, another BAR domain containing protein, and how this complex regulates secretory vesicle formation, trafficking, and refinement. Finally, Ulrik Gether (Univ. of Copenhagen) will evaluate PICK1 as a putative drug target and discuss the physiological impact of PICK1-deficiency on neuroendocrine secretion from the pituitary.

23. Neurotensin: Self-control neuropeptide and drug discovery target

Chair: Jerry Frankenheim

Presenters: Glen Hanson, Mona Boules, Ricardo Cáceda, George Uhl

Limbic/basal ganglia neurotensin (NT) systems, overall, inhibit dopaminergic (DA) activity, suggesting that activation of NT receptors may be useful in management of states of excessive DA activity, e.g., schizophrenia/addiction. Glen Hanson observed that during maintenance of methamphetamine self-administration (METH SA), an endogenous NT system is shut down through D1 mechanisms, but another NT system appears to be activated in rats that fail to SA METH. During extinction in rats that had METH SA, a NT system is activated through D2 mechanisms, eliminating lever-pressing. Thus it appears that NT systems have different roles in maintenance, extinction, and possibly reinstatement of METH SA. Mona Boules (Elliott Richelson lab) will discuss agonists of the G-protein coupled receptor subtypes (NTS1 and 2), mainly peptides related in sequence to 8- or 9-13 fragments of NT that can be given outside the brain, pass the BBB, and cause a multitude of pharmacological effects. Studies in rodents and monkeys suggest broad neuropsychiatric therapeutic uses for these compounds; risks of their adverse effects will also be discussed. Ricardo Cáceda's (Charles Nemeroff's lab) new observations on human NT gene polymorphisms and susceptibility to cocaine-induced psychosis provide further implications for the pathophysiology of psychotic disorders and drug abuse. George Uhl will document the subtle alterations in cocaine responses in heterozygous and homozygous NT gene knockout (KO) mice, which contrast with some observations with NT antagonists, and support the likelihood of adaptive changes in mice with lifelong alterations of NT expression. Differences between NT KO, +/-, and wild-type mice are prominent if the testing sessions are long, or there is no habituation prior to cocaine administration, indicating that endogenous NT plays specific roles in modulating effects of cocaine. Together, these findings support the notion that NT-like drugs may be selective vs. DA hyperactivity, sparing vital DA function.

24. Oligodendrocytes and CNS myelination: Molecular mechanisms regulating cellular morphology during development and disease

Chair: Babette Fuss

Presenters: Donna Osterhout, Timothy Kennedy, Carmen Melendez, Pamela Knapp

Oligodendrocytes, the myelinating cells of the central nervous system, undergo extensive morphological changes as they differentiate. Differentiating oligodendrocytes arise from simple, bipolar migratory oligodendrocyte progenitors that progress first into a post-migratory cells extending complex networks of cellular process and finally into mature oligodendrocytes generating the myelin sheath. These morphological changes occur during oligodendrocyte differentiation concurrently with changes in the gene expression profile. Interestingly, experimental evidence suggests that the morphological changes can be regulated by molecular mechanisms different from the ones that determine changes in gene expression. The goal of this panel will be to present novel data on molecular mechanisms affecting oligodendrocyte morphology and myelin formation. Donna Osterhout from SUNY Upstate Medical University will discuss signals that regulate oligodendrocyte process outgrowth. These signals include the Src kinase Fyn and its regulation by extracellular signals during development and after injury. Timothy Kennedy from the Montreal Neurological Institute at McGill University will be introducing the functions of Netrin-1 in regulating oligodendrocyte maturation and myelination. Carmen Melendez from Hunter College will present her data related to promoting myelin formation via manipulation of oligodendrocyte's cytoskeleton. In particular, she will be discussing *in vivo* strategies to accelerate myelin repair through inhibition of myosin II activity in oligodendrocytes. Pamela Knapp from Virginia Commonwealth University will be discussing oligodendrocyte and myelin abnormalities under pathological conditions. In particular, she will be discussing abnormalities related to HIV infection.

Talking about drugs with kids—What to say and why to say it

Chair: Karen Greif

Presenter: John Mendelson

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

25. Regulation and function of adult neurogenesis

Chair: Zhengui Xia

Presenters: Chay T. Kuo, Zhengui Xia, Xinyu Zhao, Evan Y. Snyder

Adult neurogenesis occurs in the DG and the SVZ of mammalian brains. These adult born neurons functionally integrate into the hippocampal circuitry and the olfactory bulb, suggesting the interesting possibility that adult neurogenesis may contribute to hippocampus-dependent memory formation and olfactory behavior. However, although adult born neurons have been extensively characterized at the cellular level, their functional impact on olfactory behavior and neuroplasticity is still controversial. Furthermore, signaling and molecular mechanisms regulating adult neurogenesis are not well defined. This panel will discuss mechanisms regulating adult neurogenesis and functional consequences of adult neurogenesis under normal physiological conditions as well as in the disease state. Chay Kuo (Duke University) will discuss cellular and molecular mechanisms regulating SVZ ependymal niche function, and their control of adult SVZ neurogenesis. His studies shed light on how continuous production of new neurons in the adult brain is sustained. Zhengui Xia (University of Washington) will present data on a critical role for the ERK5 MAP kinase in the regulation of adult neurogenesis in the DG and SVZ, and the functional consequence of ERK5-regulated adult neurogenesis on memory formation and olfaction. Xinyu Zhao (University of Wisconsin-Madison) will discuss genetic and epigenetic factors regulating neurogenesis, including fragile X mental retardation protein, Methyl DNA binding proteins, and microRNAs. This work unveils a role for neurogenesis in the etiology of human neurodevelopmental disorders. Finally, Evan Snyder (Sanford-Burnham Medical Research Institute) will discuss the interplay between adult neurogenesis and brain tumors, and how cell nonautonomous factors and an inappropriate neurogenic-to-gliogenic switch (mediated by MAPK and STAT signaling) can change the fate of neural stem cells from becoming neurons in the olfactory bulb to becoming a glioblastoma.

26. Blast traumatic brain injury

Chair: Barclay Morrison

Presenters: C. R. “Dale” Bass, Barclay Morrison, David Meaney

Traumatic brain injuries (TBI) have become the signature wound of current US conflicts, with approximately 212,742 documented cases since 2000; the majority are classified as mild. A majority are also caused by improvised explosive devices (IEDs). Only recently has it been accepted that the primary interaction of a blast wave with the head can cause TBI; consequently, there remains substantial disagreement about the mechanisms of blast TBI. To better understand the biomechanical and biological mechanisms, laboratory models have been established which allow for precise control of the blast physics and for in-depth study of the post-blast effects. This panel will present the latest findings in the field using a combination of both animal and in vitro models which are grounded in a deep understanding of blast physics to reproduce exposures that are scaled appropriately to represent battlefield conditions. First, C. R. “Dale” Bass (Duke University) will discuss the fundamentals of blast biomechanics, including real-world blast exposures and clinical presentation, the relationship between blast-induced TBI and pulmonary injury, and scaling from animal models to the human condition. Barclay Morrison (Columbia University) will present results from an in vitro model of blast TBI using organotypic brain slice cultures to identify tissue-level exposure limits for induction of cell death and electrophysiological dysfunction. David Meaney (University of Pennsylvania) will present multiscale studies of neuronal networks, defining how synaptic connections can be mapped in networks, their relationship to the connectome, and the regulation of changes in network topology after blast exposure.

27. Understanding and enhancing motor behavior with noninvasive brain stimulation for the benefit of healthy and stroke patients

Chair: Pablo Celnik

Presenters: Pablo Celnik, Giacomo Koch, Friedhelm Hummel

Recent years have seen a significant improvement in the understanding of the neural mechanisms underlying human motor behavior. Using transcranial magnetic stimulation (TMS), we have been able to investigate the dynamic processes that underlie motor performance and learning. For instance, changes

in excitability in primary motor cortex (M1) and between cortical regions can explain performance of reaching and bimanual movement. Similarly, LTP-like plasticity in M1 and cerebellar-M1 connectivity changes have been identified as fundamental mechanisms underlying motor learning. Importantly, how brain lesions, such as stroke, affect activity of these networks may predict the level of motor recovery. These advancements have informed the use of transcranial direct current stimulation (tDCS), another form of noninvasive brain stimulation, known to affect NMDA receptor activity. Like this, tDCS has been shown to modulate excitability of cortical and cerebellar regions affecting motor behavior. These promising findings have triggered investigations testing the effects of TMS and tDCS geared to enhance recovery of motor function in stroke patients. This panel will review the utilization of TMS and tDCS to understand human motor behavior and as therapeutic interventions to enhance motor function in healthy individual and stroke patients. Pablo Celnik (Johns Hopkins University) will review the mechanisms of TMS and tDCS and discuss the physiological mechanisms underlying motor learning and the application of tDCS to enhance human motor learning. Giacomo Koch (Fondazione Santa Lucia, Rome, Italy) will discuss studies of cortical connectivity during reaching movements in healthy individuals and patients with neglect. Finally, Friedhelm Hummel (University Medical Center Hamburg-Eppendorf) will present recent studies investigating physiological mechanisms underlying motor performance in healthy and stroke patients, and studies testing tDCS to enhance motor function after stroke.

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

28. Hemichannels in the nervous system: More than “half” the story?

Chair: Bruce Ransom

Presenters: Michael Bennett, Nanna MacAulay, Bruce Ransom

Connexin and pannexin hemichannels are emerging as novel channels in many different neurobiological settings. These channels are in an active stage of characterization and critical evaluation. This panel session will consider these channels in several different preparations. Michael Bennett (Albert Einstein College of Medicine) will discuss the induction and functions of connexin hemichannels in astrocytes under physiological and pathological conditions. His studies indicate that these channels are plastic and capable of rapid expression under the control of trophic factors and oxidative stress. Nanna MacAulay (University

of Copenhagen) will discuss connexin43 (Cx43) hemichannel behavior in the *Xenopus laevis* expression system. These studies show low Ca²⁺-induced Cx43-dependent permeability to fluorescent probes but fail to demonstrate permeability to other biological relevant molecules such as ions, water and small osmolytes. Bruce Ransom (University of Washington) will present evidence that astrocyte Cx43 hemichannels can powerfully modulate intracellular [Na⁺]. He will also discuss activity-dependent plasticity of these channels.

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

29. Deciphering a paradox: The role of the serotonin _{2A} receptor in antipsychotic action

Chair: Amelia Gallitano

Presenters: Amelia Gallitano, Caitlin McOmish, Javier González-Maeso, David Erritzoe

Since the discovery of clozapine, one of the leading antipsychotic medications developed to date, the serotonin _{2A} receptor (5-HT_{2A}R) has been hypothesized to play a key role in psychosis and its treatment. In support of this theory, 5-HT_{2A}R agonists induce hallucinations, and second-generation antipsychotics (SGAs) block 5-HT_{2A}Rs. However, several findings indicate that the role of the 5-HT_{2A}R is not so clear. Highly selective 5-HT_{2A}R antagonists show only weak antipsychotic activity in clinical trials. Recent animal studies suggest the efficacy of clozapine may be mediated by presynaptic (i.e., non-5-HT_{2A}R) actions. Finally, although some studies report increased 5-HT_{2A}R binding in schizophrenia brains, most postmortem studies show reduced 5-HT_{2A}R density in patients, particularly in frontal cortex. Dr. Gallitano (University of Arizona) has previously reported that mice lacking the schizophrenia-associated immediate early gene *Egr3* are resistant to the sedating effects of clozapine (paralleling schizophrenia patients' heightened tolerance to antipsychotic side effects). She will present data revealing that the mechanism underlying this effect appears to be a deficit in cortical 5-HT_{2A}Rs. Dr. McOmish (Columbia University) will present data showing that 5-HT_{2A}R-KO mice display the same resistance to sedation by clozapine as *Egr3*-KO mice, and that this effect is driven by cortical 5-HT_{2A}Rs and is selective for SGAs. Concluding the panel, Dr. Maeso (Mount Sinai School of Medicine) will present his findings of increased 5-HT_{2A}R expression in postmortem untreated, but not treated, schizophrenia brains. Discussion will focus on developing testable hypotheses to explain this divergence of results based on molecular mechanisms of 5-HT_{2A}R function.

30. New biological findings and treatment approaches in PTSD

Chair: Chris Reist

Presenters: Michael Hollifield, Suzy Bird Gulliver, Michael Alkire

Posttraumatic stress disorder (PTSD) is a common, debilitating, and complex disorder. Many genetic and environmental influences are important in the genesis and maintenance of PTSD. To this end, gene expression analysis is a critical technology for PTSD research to detect essential genetic output influenced by gene-environment interactions. The first presentation by M. Hollifield (Long Beach VA Healthcare System) applies gene expression analysis for achieving two aims: first to evaluate reliably expressed genes and second to identify genes that may be differentially expressed in PTSD versus an appropriate control group. Brain imaging serves as a key approach to study environmental impacts on the development of PTSD. The second presentation (S. Gulliver, Texas A&M University) reviews the use of diffusion tensor imaging to test the hypothesis that microstructural integrity of the uncinate fasciculus is altered in both TBI and PTSD. The final presentation (M. Alkire and C. Reist, Long Beach VA Healthcare System and UC-Irvine) will review innovative approaches to treatment. Stellate ganglion blockade (cervical sympathetic blockade) has been observed to rapidly reduce the hyperarousal subgroup of PTSD symptoms. This approach adds to a growing list of interventions affecting adrenergic pathways that have been shown to improve PTSD symptoms. In addition, the use of virtual reality technology is gaining significant acceptance as an aid to conducting prolonged exposure therapy, the intervention with perhaps the largest effect size. Collectively, these presentations highlight the connections between central and peripheral neural and genetic dysfunction in PTSD and ways to potentially reverse the dysfunction.

31. Magic bullets and arrows: Biological approaches to treat substance use disorders

Chair: Phil Skolnick

Presenters: Paul Pentel, Paul Bremer, Stephen Brimijoin, Tom Kosten

As for other psychiatric disorders, pharmacological approaches to treating substance use disorders (SUDs) have traditionally focused on small molecules. This approach has not yielded highly effective medications. Thus, there are no approved medications to treat stimulant (e.g., cocaine and methamphetamine) abuse, and options to treat other SUDs (including nicotine and opioids) are

far from ideal. However, in contrast to other psychiatric disorders, emerging evidence indicates biological approaches to treat SUDs are viable alternatives. The basic principle underlying these approaches is to either prevent or markedly slow the rate of entry of the abused substance into the brain. This panel will review state of the art efforts (both preclinical and clinical) to treat SUDs using biological approaches. Paul Pentel (Univ. Minn.) will review the development of nicotine vaccines, including recent clinical studies. Paul Bremer (Scripps) will present data demonstrating that a heroin vaccine can prevent both the acquisition of heroin self-administration in naïve animals and the reacquisition of self-administration in addicted rats following extinction. Stephen Brimijoin (Mayo Clinic) will describe the evolution of “engineered” esterases, mutant butyrylcholinesterases capable of metabolizing cocaine 1000-x more effectively than the wild type enzyme. Recent gene transfer experiments in rats indicate a single such treatment with cocaine hydrolase provides at least six months of protection against resumption of drug-seeking behavior triggered by re-exposure to cocaine. Tom Kosten (Baylor) will present Phase 2 studies of a human cocaine vaccine and describe preclinical studies using cocaine vaccines with improved immunogenicity compared to the vaccine currently in clinical trials.

Panel • Tuesday, 7:30–9:30 AM • Magpie

32. Homeostatic and reward mechanisms involved in the neural regulation of energy homeostasis and obesity

Chair: Barry Levin

Presenters: Barry Levin, Catherine Kotz, Emily Noble, Brian Baldo

The brain is the ultimate regulator of energy homeostasis, the balance among intake, expenditure, and storage of calories. To do this, it requires inputs from the internal and external environments in the form of neural, hormonal, metabolic “homeostatic” inputs from the body on the one hand and emotional, cognitive, and reward cues on the other. These signals are incorporated into a distributed network of specialized neurons in various brain areas that integrate these signals and activate neurohumoral, autonomic, and motor systems involved in all aspects of energy homeostasis. Barry Levin will provide an overview of the various systems involved in this network and describe how specialized metabolic sensing neurons respond to cues from the periphery and how their function is affected by genetic and environmental perturbations and obesity. Catherine Kotz will discuss the relative importance of physical activity in body weight regulation, as well as recent findings indicating that brain orexin activity is associated with increased physical activity, which prevents weight gain in an animal model of obesity resistance. Emily Noble will discuss

the role of BDNF in specific hypothalamic nuclei to promote negative energy balance by both inhibiting food intake and increasing energy expenditure and how environmental enrichment and voluntary wheel running reduce feeding and body weight, possibly via a BDNF signaling. Brian Baldo will describe the anatomy and function of neural systems (emphasizing nucleus accumbens and prefrontal cortex) that respond to the rewarding properties of food to drive animals to eat beyond their homeostatic needs as one potential factor leading to the development of obesity.

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

33. New approaches to probe pathology in the human brain

Chair: Gregory Ordway

Presenters: Scott Russo, Stephen Ginsberg, Wolfgang Sadee,

Mirjana Maletic-Savatic

Rapidly advancing technologies are accelerating the pace of discovery of the molecular and cellular pathology of neurological and psychiatric diseases. This panel will explore novel approaches to study human brain pathology, emphasizing cutting-edge methods and reverse-translation of human findings using animal and cell models. Scott Russo will describe the use of parallel multiplex enzyme-linked immunosorbent assays to discover elevations of blood interleukin 6 (IL6) in major depression, and similar IL6 elevations in blood and brain of socially defeated mice. Brain infusions of IL6 promoted depressive-like behavior in mice leading to testing of novel anti-inflammatory agents for antidepressant activity. Stephen Ginsberg will show how typical brain microarray studies err as a result of a dilution effect on underrepresented cells within a dissection region. Microarray analysis of single cell populations captured by laser microdissection permitted discovery of altered expression of genes related to neuronal endosomal function in CA1 neurons in subjects with preclinical Alzheimer's disease. Results of overexpression studies with human fibroblasts imply that increased endocytic pathway activity contributes to neurotrophic signaling deficits during Alzheimer's disease progression. Wolfgang Sadee will discuss the use of RNA expression profiles determined using gene by gene and genome-wide approaches to discover new regulatory splice variants, 3' and 5' UTRs. These methods demonstrate robust abnormalities in expression profiles and reveal a gene-gene-environment interaction in the brains of cocaine abusers. Mirjana Maletic-Savatic will discuss the use of proton magnetic resonance spectroscopy to identify a metabolic biomarker of neural stem/progenitor cells and to measure metabolites present at very low concentration in the live human brain, an approach with great potential to delineate biochemical and cellular pathways impaired in psychiatric and neurological diseases.

34. Dynamic regulation of glutamatergic synapses: From mechanisms to functional consequences

Chairs: Hey-Kyoung Lee, Andres Barria

Presenters: Andres Barria, Karen Zito, Lu Chen, Hey-Kyoung Lee

Excitatory synaptic transmission in the central nervous system of mammals is mediated by glutamate and its receptors. Glutamatergic synapses undergo dynamic regulation both structurally and functionally, which is necessary for proper cortical circuit development and experience-dependent synaptic plasticity. Hence, understanding the processes regulating glutamatergic synapses has wide implications for critical brain functions such as learning and memory, brain development, and neuropathology. This panel will focus on regulatory mechanisms used at glutamatergic synapses for proper synaptogenesis and homeostatic adaptation to changes in neural activity. Andres Barria (U Washington) will first discuss how the developmental switch in NMDA receptor subunit composition affects synapse maturation and stabilization during development via recruiting appropriate signaling and scaffolding proteins. New spines are capable of rapid functional maturation and incorporation into structurally mature synapses, implying that even short-term spine growth may result in functional changes in neural circuits. Karen Zito (UC Davis) will discuss how synaptic activity-dependent regulation of proteasomal degradation promotes the growth of new dendritic spines. Functionally mature synapses also need to retain the ability to constantly adjust to the overall neural activity for proper brain functions. Lu Chen (Stanford U) will talk about how period of inactivity leads to homeostatic adaptation of excitatory synapses. She will present data showing that synthesis of all-trans retinoic acid (RA) is regulated by dendritic Ca²⁺ signaling. Hey-Kyoung Lee (Johns Hopkins U) will then discuss how sensory experience homeostatically regulates excitatory synapses in sensory cortices, and how this relates to cross-modal sensory compensation. Thus, this panel will cover the dynamics of activity-dependent excitatory synapse regulation ranging from specific molecular mechanisms to functional consequences *in vivo*.

35. The Habenula: At the crossroads of circuits mediating addiction and depression

Chair: Fritz Henn

Presenters: Martine Mirrione, Ramiro Salas, Wayne Drevets, Fritz Henn

The habenula has recently been the focus of increasing attention in the pathology of a variety of psychiatric illnesses. The basic work in recent years has clearly shown that the habenula plays a role in reward, in disappointment and controls the output of all aminergic midbrain nuclei. Martine will review the circuit that appears to mediate learned helplessness, an animal model of depression. Using both animal PET and histological tracing, she will outline the critical role of the habenula in this circuit. Ramiro will review the evidence for the habenula in addiction and present data using his fMRI task to look at habenular activity in addiction. Wayne will look at imaging the habenula in depression using both PET and ASL MR studies and demonstrate changes both in the induction of depression and in its treatment. Fritz will review the details of the circuit in depression and discuss its role as a new target for deep brain stimulation in treatment-resistant depression, including both animal and human studies.

36. Encoding motivation and arousal in the brain: Neuropeptide regulation of catecholamine systems

Chair: Julia Lemos

Presenters: Rita Valentino, Julia Lemos, Luis de Lecea, Stephanie Borgland

A cardinal feature of the most prevalent and debilitating psychiatric pathologies (i.e., depression, anxiety, and addiction) is dysfunction in motivated behavior and arousal. As such, it is critical to understand the neurochemicals and physiology involved in mediating these aspects of behavior and how they become dysregulated in models of psychiatric disease. Neuropeptides are released from the hypothalamus as well as from limbic brain regions in response to salient stimuli (both appetitive and aversive) that the organism may encounter as it engages in the environment. These act on catecholamine systems to promote arousal and goal-directed behaviors. The central goal of this panel is to elucidate physiological and, in turn, behavioral consequence of neuropeptide regulation of catecholaminergic systems. Moreover, this panel will highlight the corticotropin-releasing factor (CRF) and hypocretin neuropeptide systems;

two neuropeptide systems that have been heavily implicated in addiction- and depression-like behavior in preclinical models. Rita Valentino (Univ. of Pennsylvania) will present data on the regulation of the brain norepinephrine system by CRF in the arousal and cognitive aspects of the stress response. Julia Lemos (Univ. of Washington) will discuss CRF-mediated regulation of dopamine release in the nucleus accumbens in naïve and stress-exposed animals and how this interaction facilitates motivated behavior. Luis de Lecea (Stanford University) will discuss recent data from his laboratory on the role of the connection between the hypocretin system in the hypothalamus and the locus coeruleus and their role in regulating sleep-to-wake transitions. He will also discuss the use of combinatorial optogenetics to functionally dissect interactions between peptides and monoaminergic systems. Stephanie Borgland (Univ. of British Columbia) will present data on the effects of hypocretin on drug-induced synaptic plasticity in dopaminergic VTA neurons.

Special Session • Tuesday, 9:45-11:15 AM • Ballroom 1

In honor of Bart Hoebel: A giant for 50 years in the field of food and drug reward

Chair: Sarah Leibowitz

Presenters: Friedbert Weiss, George Koob, Charles O'Brien

Panel • Tuesday, 4:30-6:30 PM • Ballroom 1

37. To ski or not to ski: Dopamine's role in value-guided decision making

Chair: Paul Phillips

Presenters: Jeff Beeler, Sean Ostlund, Paul Phillips, Saleem Nicola

A common notion in neuroscience is that dopamine neurotransmission is used to guide choices between alternative available actions based upon the value of their potential outcomes. While many investigators agree that dopamine is involved in this type of decision making, its specific role in modulating choices is not well established. This panel will address these shortcomings in the current literature by presenting behavioral data from rodents in experiments using genetic and pharmacological manipulations and those collecting electrophysiological and neurochemical correlates of behavior. First, Jeff Beeler (University of Chicago) will present data investigating how dopamine modulates the balance between exploration and exploitation to adapt energy expenditure and distribution to environmental conditions. Sean Ostlund (University of California, Los Angeles) will discuss his studies addressing the contribution of dopamine to the activational properties of Pavlovian stimuli on instrumental behavior and their

ability to bias action selection. Next, Paul Phillips (University of Washington) will present data from reward devaluation studies, examining the time course over which dopamine-encoded valuation signals and choices are updated. Finally, Saleem Nicola (Albert Einstein College of Medicine) will present work demonstrating dopamine-dependent encoding of reward prediction and behavioral response latency by medium spiny neurons in the nucleus accumbens.

Panel • Tuesday, 4:30–6:30 PM • Magpie

38. Neuroepigenetic and neurotrophic control of the prefrontal-accumbens circuit in response to stress and drugs

Chair: Jacqueline McGinty

Presenters: Courtney Miller, Herb Covington, Jacqueline McGinty, Ghazaleh Sadri-Vakili

Addictive drugs and stress cause changes in gene and protein expression in the prefrontal-accumbens circuit that have persistent behavioral consequences. Recently, epigenetic alterations such as histone methylation and acetylation have been implicated in these drug- and stress-induced behavioral changes. One of the common targets of epigenetic regulation in response to stress and drugs of abuse is BDNF-TrkB-CREB signaling. In this panel, the role of epigenetic regulation and BDNF signaling in prefrontal-accumbens circuitry in animal models of psychostimulant abuse and social defeat stress will be discussed. Courtney Miller (Scripps Res Institute, FL) will discuss recent findings indicating an important role for the histone H3K4 demethylase and transcriptional repressor, *smcx*, encoded by an X-linked mental retardation gene, in the regulation of methamphetamine-seeking behavior through interactions with other epigenetic modifications in the accumbens. Herb Covington (Duke University) will present data on the role of histone H3 K9 dimethylation (H3K9me₂) in the medial prefrontal cortex and accumbens in vulnerabilities to social stress following exposure to drugs of abuse. Jacqueline McGinty (Med Univ SC) will discuss findings that BDNF infusion into the prefrontal cortex reverses cocaine-induced disturbances in ERK and CREB phosphorylation in the PFC during early withdrawal as a critical step in restoring homeostatic regulation of the PFC-accumbens pathway leading to suppression of cocaine-seeking. Ghazaleh Sadri-Vakili (Harvard University) will discuss the role of prefrontal cortex BDNF in the development of a cocaine-resistant phenotype in the male offspring (F1 and F2 generations) of rodents exposed to cocaine prenatally or via self-administration. These presentations will highlight the critical role of epigenetics and their targets in shaping persistent and possibly heritable responses to chronic stress and addictive drug exposure.

39. Stem cell: From altered biology to cell-replacement therapy

Chair: Susanna Rosi

Presenters: Susanna Rosi, Fulton Crews, Miles Herkenham, Cesar Borlongan, Charles Limoli

The brain contains neural stem cells formed throughout life that may play important roles in cognition, memory, and repair. Adult-born stem cell fate and function can be affected by pathological and pathophysiological factors. The mechanisms of altered stem cell proliferation and migration are largely unknown although there is promise for therapeutic intervention. This session will discuss recent work on altered stem cell biology following inflammation, stress, and injury and will report evidence for stem cell replacement as a therapeutic approach for cognitive dysfunctions. Dr. Susanna Rosi (UCSF) will talk about how inflammation alters the functional integration of the adult-born neurons into hippocampal circuits and will discuss the role of the chemokine receptor CCR2 in altered stem cell function. Dr. Fulton Crews (UNC) will talk about HMGB1 signaling through Toll-Like Receptors, regulating neuroinflammation and reducing hippocampal neuroprogenitor cell survival and differentiation to glia. He will present data on the effects of naltrexone and antidepressants on stem cell biology. Dr. Miles Herkenham (NIMH) will provide evidence that behavioral manipulations such as environmental enrichment and psychological stress affect stem cell production in the hippocampus with functional consequences on the expression of depressive-like behaviors. Dr. Cesar Borlongan (USF) will discuss how stroke-induced neuroinflammation can mobilize stem cells. He will talk about the cytokine/chemokine signaling pathways, in particular the SDF-1 and CXCR4 system, as robust migratory cues that can be utilized for trafficking of stem cells from the periphery to the ischemic site of injury. Finally, Dr. Charlie Limoli (UCI) will show how engraftment of stem cells can protect the brain from side effects of cranial irradiation. He will discuss the application of human neural stem cell transplant therapy to ameliorate cognitive dysfunctions.

40. New insights to modulation of ionotropic glutamate receptor function

Chair: Kasper B. Hansen

Presenters: Frank Menniti, Kasper B. Hansen, David S. Brecht, Geoffrey T. Swanson

Ionotropic glutamate receptors, which include NMDA, AMPA, and kainate receptors, are central to the fundamental brain processes of neuronal development, learning, and memory but are also implicated in a wide array of neurological problems, including epilepsy and ischemic brain injury, and some neuropsychiatric conditions. For these reasons, glutamate receptors are receiving considerable interest as targets for new therapeutic agents. The first two presentations in this panel will focus on modulation of NMDA receptor function. Frank Menniti will provide a general overview of the therapeutic potential of glutamate receptor modulators, with emphasis on GluN2B-targeted negative NMDA receptor modulators and the development of new classes of modulators for the treatment of a variety of CNS disorders. Kasper B. Hansen will discuss structural determinants and mechanism of action for a new GluN2A-selective NMDA receptor antagonist, and how this data suggest a previously unrecognized binding site that can be exploited to allosterically inhibit receptor function. The last two presentations in this panel will focus on modulation of AMPA and kainate receptor function by transmembrane accessory proteins. We know that transmembrane AMPA receptor regulatory proteins (TARPs) regulate both trafficking and biophysical properties of AMPA receptors, as well as have profound effects on receptor pharmacology. David S. Brecht will discuss regulation of AMPA receptor function by cornichon proteins, a newly identified class of accessory proteins that modulate AMPA receptor-TARP assembly. Finally, Geoffrey T. Swanson will show data demonstrating modulation of kainate receptors by NETO proteins, and discuss how the presence of these accessory proteins could influence kainate receptor function in the brain. These presentations will provide a comprehensive discussion of glutamate receptor modulation and recent advances in our understanding of glutamate receptor structure and function.

41. Opioid receptors: Binding, activation, phosphorylation, and desensitization

Chair: John Williams

Presenters: Michelle Zedlitz, William Birdsong, Matthew Banghart, Shane Hentges

The development of tolerance to morphine and other opioid agonists is a major problem in the use of opioids for pain management. Multiple mechanisms are thought to contribute to tolerance at the cellular and systems level. This panel will present the current knowledge of first steps in the progression of agonist/receptor interaction that eventually lead to cellular tolerance and new technical approaches to study these processes. Michelle Zedlitz (UCSF) will present results showing the phosphorylation pattern of the mu-opioid receptor following agonist treatment. Will Birdsong (OHSU) will present imaging results measuring changes in agonist binding affinity following a treatment that causes acute desensitization. Matthew Banghart (Harvard) will present the development and use of photoactivatable enkephalin for the rapid and spatially-delimited application of opioids in brain slices. Shane Hentges (Colorado State) will show how opioids differentially induce desensitization at pre- and postsynaptic receptors.

42. Alzheimer's disease: Pathology and treatment in animal models

Chair: Isabelle Aubert

Presenters: Michael Kawaja, Isabelle Aubert, JoAnne McLaurin, Henriette van Praag

Alzheimer's disease (AD) is characterized by cognitive deficits, amyloid-beta peptides accumulation, tau pathology, and neuronal loss in several brain regions. This panel will address challenges and successes in recapitulating AD pathology and developing treatments in animal models of AD and translating them to clinical settings in AD patients. Dr. Kawaja (Queen's University) will provide an introduction to AD, and he will present his recent findings related to amyloid-beta-induced proteomic changes in mouse models of AD and the identification of a novel protein not previously described in AD. Dr. Aubert (Sunnybrook Research Institute) will discuss transcranial magnetic resonance-guided focused ultrasound (MRIgFUS) technology used to nonsurgically deliver therapeutics from the bloodstream to the brain. Her talk will include the effects of FUS drug delivery and FUS alone benefits in TgCRND8 mice, which could lead to a resolution of disease pathology and the potential for translation

to clinical settings in the future. Dr. McLaurin (University of Toronto) will present new data on scyllo-inositol, which is entering Phase III clinical trials for AD. Her previous work demonstrated that scyllo-inositol ameliorates disease pathology and cognitive functions in TgCRND8 mice. She extended these studies to demonstrate the rescue of neurovasculature structure and function as a result of scyllo-inositol treatment. Gene expression changes as a function of scyllo-inositol treatment highlight novel target pathways for intervention. Henriette van Praag (NIA) will present data pertaining to long-term exercise and antidepressants (fluoxetine) as a potential therapeutic intervention. Effects of wheel running and fluoxetine on hippocampal neurogenesis, neurotrophin levels, amyloid-beta and tau pathology, as well as behavior in 3xTg-AD and non-Tg mice, will be presented.

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

43. Integration of information in the nucleus accumbens and reward-based behaviors

Chair: Patricio O'Donnell

Presenters: Bruce Hope, Garret Stuber, Gwendolyn Calhoon, Michael Cohen

The nucleus accumbens (NA) is critically involved in reward processing and goal-directed behaviors. This brain region receives convergent glutamatergic inputs from the hippocampus, basolateral amygdala (BLA), and prefrontal cortex (PFC), as well as a dense dopamine (DA) innervation from the ventral tegmental area. The manner these inputs are integrated and their modulation by DA may determine behavioral outcomes. This panel will address recent work on the impact of several different afferents to the NA on neural activity and behavior. Bruce Hope will present data on neuronal ensembles in the NA selected by environmental stimuli that mediate learned associations between drugs of abuse and the environment where drugs are injected. Unique molecular and synaptic alterations within these ensembles may contribute to the formation and maintenance of learned associations. Garret Stuber will discuss the role of BLA and PFC projections to the NA in natural rewards using optogenetic tools. Optical stimulation of BLA, but not PFC fibers, reinforces reward-seeking, and optical BLA inhibition reduces cue-evoked sucrose intake, demonstrating an important role of the BLA-NA pathway in naturally occurring reward-related behavior. Gwen Calhoon will present in vivo intracellular recordings in rat NA showing that bursts of stimuli to the PFC attenuate responses to hippocampal inputs, suggesting that strong PFC activation can override ongoing activity driven by other inputs. Michael Cohen will present human data showing that electrophysiological functional connectivity between the NA and PFC are

characterized by stronger top-down directionality (PFC → NA), are maximal in the delta-theta frequency band (~2–8 Hz), and are modulated by reward anticipation. The data converge in showing reward-related activity in the NA, characterized by neuronal ensembles and tightly modulated by PFC and BLA inputs.

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

44. How drugs of abuse alter the function of metabotropic glutamate receptors: Behavioral and molecular evidence

Chair: Marek Schwendt

Presenters: Friedbert Weiss, Foster Olive, Marek Schwendt, John Q. Wang

One of the greatest challenges in addiction treatment is to minimize motivational and cognitive deficits resulting from chronic drug abuse. It is believed that these impairments arise from persistent region-specific neuroadaptations. A number of pharmacological studies have established that brain mGluR receptors play a critical role in mediating the reinforcing effects of most abused drugs, and thus manipulation of these receptors can prevent or at least attenuate relapse-like behaviors (i.e., reinstatement) in animal models. However, despite the progress in developing specific ligands for individual mGluR subtypes, our knowledge of drug-induced changes in mGluR function remains limited. This session will discuss various drug-induced adaptations in the function of individual mGluR receptors from cellular and behavioral perspectives. First, Dr. Friedbert Weiss will present data demonstrating increased functional activity of mGluR2/3 receptors in the nucleus accumbens in regulating EtOH-seeking in dependent rats vs. nondependent rats. In contrast, a decrease in mGluR5 function occurring with EtOH-dependence suggests a dysregulation of pre- and postsynaptic mechanisms of cortico-striatal glutamate neurotransmission. Second, Dr. Foster Olive will present novel data indicating that chronic methamphetamine treatment changes the role of mGluR5 receptors in the nucleus accumbens in regulating brain reward function as measured by intracranial self-stimulation (ICSS). Next, Dr. Marek Schwendt will discuss his findings on regulation of mGluR2/3 and mGluR7 trafficking by self-administered methamphetamine. He will also present data on the relation between decreased mGluR2/3 surface expression and methamphetamine-induced memory deficits. Finally, Dr. John Wang, will present neurochemical evidence on the mechanism of ERK-mediated mGluR5 phosphorylation and how this mechanism is altered in amphetamine-treated animals.

45. Therapeutic roles of histone deacetylase (HDAC) inhibition in neurological disorders

Chair: Elizabeth Thomas

Presenters: Santosh R. D'Mello, Curt Freed, Fred Maxfield, George Rogge

Histone deacetylases (HDACs) enzymes, which affect the acetylation status of histones and other important cellular proteins, have been recognized as potentially useful therapeutic targets for a broad range of human disorders. Emerging studies have demonstrated that different types of HDAC inhibitors show beneficial effects in various experimental models of brain diseases. While HDAC inhibitors are known to alter chromatin structure resulting in changes in gene transcription, understanding the exact mechanisms for the clinical efficacy of these compounds remains a challenge. HDAC inhibitors have been shown to exert neuroprotective effects, improve learning and memory, and reverse a variety of disease phenotypes in model systems. The HDACs comprise a large family of proteins, with 18 HDAC enzymes currently identified in humans. Hence, an important question for HDAC inhibitor therapeutics is which HDAC enzyme(s) is/are important for disease phenotype amelioration, as it has become clear that individual HDAC enzymes play different biological roles in the brain. This panel will discuss the latest findings on the roles of HDAC inhibition as it relates to neurodegenerative and neurological disorders and isoform-specific effects of individual HDACs in the brain. Following an introduction to the topic by Elizabeth Thomas (The Scripps Research Institute), Santosh R. D'Mello (University of Texas, Dallas) will discuss the roles of individual HDAC enzymes in neuroprotection and neurodegeneration. Secondly, Curt Freed (University of Colorado School of Medicine) will present data showing beneficial effects of HDAC inhibitors in Parkinson's disease. Thirdly, Fred Maxfield will present data on selective HDAC inhibitors in preventing cholesterol storage defects as it relates to Niemann-Pick disease, type C. Finally, George Rogge (University of California, Irvine) will present data demonstrating a specific role of HDAC3 inhibition in drug-seeking behavior.

46. Molecular mechanisms regulating synaptic signaling in health and disease

Chair: Josef Kittler

Presenters: Josef Kittler, Katherine Roche, Roger Nicoll, Nicholas Brandon

NMDA receptors, AMPA receptors and GABAA receptors are ligand gated ion channels that, respectively, mediate fast excitatory and inhibitory synaptic

transmission in the brain, and play an essential role in regulating neural processing and brain excitability. The subunit-specific localization and stabilization of neurotransmitter receptors at synapses and their movement between synaptic and extrasynaptic sites and between surface and intracellular compartments has emerged as an important mechanism for regulating synapse composition and strength in addition to cell excitability and neuronal plasticity. However, the molecular basis of this regulation remains poorly understood, and even less is known regarding how disruption of these processes may contribute to neurological and neuropsychiatric disease. This panel will discuss recent advancements in our understanding of the signalling pathways that regulate the molecular composition and function of excitatory and inhibitory synapses and the role played by protein interactions, phosphorylation and receptor subunit specificity for tuning synaptic signalling. Roger Nicoll will discuss the use of conditional KO mice for the molecular dissection of the postsynaptic density, focusing in particular on the role of synaptic NMDA receptor subunits. Katherine Roche will discuss the subunit-specific regulation of NMDA receptor trafficking focusing on the phospho-dependent regulation of NMDA receptor subunit interactions with key scaffold and trafficking machinery by protein kinases. Nicolas Brandon will focus on the role of the schizophrenia-associated TNK kinase at excitatory synapses and its role in regulating AMPA receptor membrane trafficking and synaptic stability. Finally, Josef Kittler will present studies on the identification of a novel scaffold that regulates the synaptic accumulation and membrane trafficking of GABAA receptors and the strength of inhibitory synapses.

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

47. The locus coeruleus-norepinephrine system and stress: From behavioral flexibility to psychopathology

Co-Chairs: Vaishali Bakshi, Craig Berridge

Presenters: Rita Valentino, Vaishali Bakshi, David Devilbiss, David Morilak

Noradrenergic (NE) dysfunction is linked to psychiatric illness, but the manner in which discrete locus coeruleus (LC)-NE circuits participate in stress-induced cognitive effects is not well understood. We show evidence that redefines views of LC-NE system function and establishes links to psychopathology. Rita Valentino will describe effects of the stress peptide, corticotropin-releasing factor (CRF) on spontaneous and sensory-evoked activity of LC neurons, and effects of intra-LC CRF on attentional set shifting and markers of neuronal activation in prefrontal cortex (PFC). The ability of CRF to modulate LC activity during stress and the translational relevance of these effects to behavioral flexibility

will be discussed. Vaishali Bakshi will show that intense psychological stress engenders lasting disruptions of sensorimotor gating, and will provide evidence that such information-processing deficits are mimicked by direct pharmacological stimulation of LC or by stimulation of NE receptors in PFC. David Devilbiss will discuss effects of stress on neuronal spike trains from the prelimbic region of PFC (pPFC) of rats performing a working memory task, and show that stress suppresses the ability of pPFC neurons to represent extrinsic task-related information and degrades information retention by PFC neuronal networks. David Morilak will describe the modulatory influence of NE transmission in PFC on cognitive flexibility during stress adaptation and chronic stress-induced pathology, and as a substrate for both traditional and novel pharmacotherapeutic approaches, and non-pharmacological behavioral interventions for the treatment of stress-related psychiatric disorders. Collectively, these results suggest a prominent role for NE projections from LC to PFC in several cognitive domains that are dysregulated in psychiatric illnesses including schizophrenia, ADHD, and anxiety disorders, and illustrate how stress might have deleterious effects through this pathway.

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

48. DApleted: What does partial dopamine loss do to basal ganglia function?

Chair: Kristen Keefe

Presenters: Martin Darvas, Christopher Howard, Kristen Keefe, Jakob Dreyer

While it is clear that dopamine (DA) is essential to the functioning of the basal ganglia, questions remain about the specific nature of the role played, particularly with respect to the sensitivity of basal ganglia functions to dopamine signaling in different subregions of the striatum, as well as to partial loss of the dopamine innervation. The goal of this panel is to discuss these aspects of DA signaling in the basal ganglia, with an eye toward better understanding nuances of dopamine signaling in various disease states. Martin Darvas (University of Washington) will present data from genetically modified mice illuminating the role of DA signaling in striatal subregions on cognitive functions of the basal ganglia. Christopher Howard (Illinois State University) will discuss the effects of partial loss of striatal dopamine innervation secondary to methamphetamine-induced neurotoxicity on tonic vs. phasic dopamine signaling. Kristen Keefe (University of Utah) will then present data on the impact of such partial dopamine loss induced by methamphetamine on molecular, cellular, and systems-level functions of the basal ganglia. Finally, Jakob Dreyer (University of

Copenhagen) will present computational modeling data regarding the influence of different forms of dopamine signaling on D1 and D2 dopamine receptors and how such signaling might be affected by partial loss of the dopamine innervation of the striatum. The presentations will be followed by a period of discussion focused on the implications of these findings for better understanding the function of dopamine in the basal ganglia and for better managing the motor and cognitive sequelae of basal ganglia disorders, such as those seen in Parkinson's disease.

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

49. Is it all Mother's fault? Fetal human brain development and schizophrenia

Chair: Thomas Hyde

Presenters: Nenad Sestan, Carlo Colantuoni, Amanda Law, Thomas Hyde

The neurodevelopmental hypothesis of schizophrenia holds that this disorder results from subtle brain abnormalities beginning in utero or infancy, caused by a combination of deleterious genetic and/or environmental factors. These relatively silent abnormalities eventually interact with normal maturational processes of the brain, leading to a constellation of signs and symptoms collectively known as schizophrenia. Schizophrenia usually presents in late adolescence or early adulthood. To understand how genetic and environmental factors might affect brain growth and development, they can be studied in non-psychiatric control subjects across the lifespan, with a particular focus before the typical age of onset of illness. Dr. Nenad Sestan will talk about how human-specific features of brain development may have increased our susceptibility to major psychiatric disorders, based upon his studies of human fetal brain development. Dr. Carlo Colantuoni recently has observed specific human in utero gene expression patterns that are reversed during the first months of postnatal life. He will present novel data exploring the functional significance of these changes as they occur in utero, infancy, childhood, and adolescence. Dr. Amanda Law will present data examining the influence of risk-associated genetic variation on gene splicing and expression in key neurodevelopmental networks (i.e., NRG1, NRG3, ErbB4, NRXN1) during human fetal brain development. Factors influencing differential gene regulation in the fetal versus adult brain will be discussed in the context of schizophrenia. Dr. Thomas Hyde will discuss his work on the association between human fetal nicotine exposure and gene expression, as model of adverse environmental effects on human brain development.

50. Behavioral disinhibition, drugs, and brain dysfunction: Chicken and egg in rat and human

Chair: Thomas Crowley

Presenters: Susan Young, Thomas Crowley, Kathryn Cunningham, Barry Setlow

Shared genetic mechanisms underlie comorbidity in antisocial behavior, substance use disorders (SUD), impulsivity, and ADHD; considered together as behavioral disinhibition (BD), those disorders' joint heritability is 0.8. BD-related behaviors at ages 3 to 5 years predict SUD and criminality at age 32. P300 abnormalities among alcoholics' children (before any drinking) predict later SUD and antisocial problems, suggesting that BD begins with early-onset, persisting brain abnormalities. Then, when SUD develops in persons with BD, the drugs exacerbate brain dysfunction, worsening the BD. Fortunately, animal models (e.g., differential reinforcement of low rates of response, one-choice serial reaction time, delay discounting) may disentangle BD's antecedent brain abnormalities from subsequent drug-induced abnormalities. Therefore, we address BD-related brain dysfunction in humans and rodents. Susan Young (University of Colorado) introduces human research in BD, presenting her well-replicated longitudinal twin studies. Thomas Crowley's (University of Colorado) fMRI data show impaired neural function as adolescent patients with antisocial substance problems (i.e., BD) contemplate doing cautious or risky actions. Kathryn A. Cunningham (University of Texas Medical Branch) demonstrates individual differences in impulsivity resulting from a homeostatic imbalance in nucleus-accumbens serotonin 5-HT_{2A} and 5-HT_{2C} receptors. She discusses novel pharmacotherapeutic strategies that would aim to restore 5-HT_{2AR}:5-HT_{2CR} homeostasis, repairing neural deficits and ameliorating impulse control disorders. Barry Setlow (University of Florida) reviews data from a rodent model suggesting that (a) individual differences in risk-taking (which are linked to corticostriatal dopamine signaling) predict later cocaine self-administration, and (b) chronic cocaine self-administration may cause lasting elevations in risk-taking and impulsivity.

51. Neurobiology of affective resilience: New insights from social defeat models

Chair: Olivier Berton

Presenters: Olivier Berton, Richard Gustin, Vincent Vialou, Kafui Dzirasa

Why does exposure to interpersonal violence precipitate the onset of PTSD and depression in a proportion of individuals and spare others from persistent

affective sequelae? Studies in rodents subjected to intraspecific aggression (i.e., Social Defeat, SD) have identified a number of SD-induced behavioral alterations that recapitulate key endophenotypes of human stress-linked affective disorders. The most robust of these alterations is an enduring form of social avoidance, reported in about 70% of SD-exposed mice, that responds to clinically effective antidepressants. This behavioral endpoint has gained acceptance in recent years as a criteria to segregate experimental populations of mice into resilient and vulnerable cohorts for neurobiological studies. This session assembles 4 junior investigators sharing this experimental paradigm and applying multidisciplinary approaches to dissect the cellular underpinnings of social avoidance and resilience to SD. Olivier Berton (University of Pennsylvania) will provide an overview of SD models and present data establishing the cytoplasmic deacetylase HDAC6 as a novel therapeutic target for resilience enhancement and a key regulator of GR chaperoning in the brain. Richard Gustin (Chavkin Lab, University of Washington) will review data implicating K opioid receptor-mediated signaling in dysphoric effects of SD and will discuss the effectiveness of K receptor antagonism in reversing established social avoidance. Vincent Vialou (Nestler Lab, Mount-Sinai Med Center) will discuss the role of the prefrontal cortex in resilience and report on data involving chromatin-mediated regulation of CCK receptors within this brain area. Kafui Dzirasa (Duke University) will report on the identification, using multielectrode recordings in freely moving mice, of social cue-induced corticolimbic synchrony patterns that provide highly predictive neural signatures for SD vulnerability.

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

52. Estrogenic modulation of metabotropic receptor function and the associated behaviors regulated by their activation

Chair: Edward Wagner

Presenters: Jill Becker, Kevin Sinchak, Edward Wagner, Nancy Muma

Estrogens exert far-reaching effects on mammalian biology—from regulating energy balance and reproductive behavior to modulating drug reward. While many of these actions can be attributed to influences on gene transcription and protein synthesis following the activation of estrogen receptor (ER) α and ER β , it is becoming increasingly well recognized that membrane-delimited estrogenic signaling also is important. Both ER α and ER β can be tethered to the plasma membrane, and there is compelling evidence for a Gq-coupled membrane ER that is neither ER α nor ER β . In addition, there is another estrogen-binding, G protein-coupled receptor termed GPR30. Activation of any of these membrane-associated ERs rapidly increases intracellular Ca $^{2+}$ and activates a myriad of

different signal transduction cascades that serves largely to alter the coupling of metabotropic receptors to their effector systems. This session explores our current understanding of how rapid estrogenic signaling influences Gi/o-coupled receptor function to ultimately bring about behavioral change. Jill Becker (University of Michigan) will discuss her findings on the estrogen-induced enhancement of dopaminergic signaling in the basal ganglia, and how this helps promote sexual behavior and impart increased vulnerability to CNS stimulant abuse. Kevin Sinchak (California State University, Long Beach) will present his work on how estrogens influence the orphanin FQ (nociceptin)/ORL1 system to prime reproductive circuitry and thereby promote sexual behavior. Edward Wagner (Western University of Health Sciences) will report on the signal transduction mechanisms underlying the estrogenic antagonism of cannabinoid-evoked changes in energy balance. Finally, Nancy Muma (University of Kansas) will talk about her recent work on the role of GPR30 in the estradiol-induced desensitization of hypothalamic 5-HT_{1A} receptor signaling, and how this desensitization may be beneficial for SSRI therapeutic efficacy.

Panel • Wednesday, 4:30–6:30 PM • Superior A

53. Cannabinoids and motivation: New insights on an old tale

Chair: Joseph Cheer

Presenters: Tommy Pattij, Eliot Gardner, Sara Ward, Giovanni Hernandez

Cannabinoids are important mediators of motivation. For example, these molecules can increase motivational drive to consume natural rewards such as food. Conversely, blockade of central cannabinoid receptors can decrease an animal's motivation for natural and drug reinforcement. Potentiation of motivational circuits and signaling transduction pathways is likely responsible for findings that cannabinoids modulate motivation. In this panel, we will discuss exciting data showing novel ways through which cannabinoids affect motivated behaviors. First, Tommy Pattij will focus on endocannabinoid signaling in different forms of impulsivity. He will present data demonstrating that tonic activation of CB1 receptors modulates inhibitory response control and that antagonists of this receptor attenuate amphetamine-induced deficits thereof. Next, Eliot Gardner will tackle the issue of the function of CB2 receptors in the brain, as this has been the subject of much debate. He will show that systemic, intranasal or local accumbal administration of a selective CB2 receptor agonist dose-dependently inhibits intravenous cocaine self-administration, cocaine-enhanced locomotion, and cocaine-enhanced accumbens extracellular dopamine in control and CB1 receptor knockout mice but not in CB2 knockout mice. Sara Ward will then talk about the relationship between pain-depressed behaviors, such as lack of motivation and cannabinoids. She will demonstrate that treatment with a

chemotherapeutic agent decreases motivation for palatable food and how this pain-depressed behavior is reversed by cannabidiol treatment. Finally, Giovanni Hernandez will discuss data showing that profound decreases in the strength of encoding of single-unit activity patterns and rapid gamma oscillations in the accumbens accompanies the effects of CB1 receptor blockade, suggesting that the endogenous cannabinoid system plays an important role in sculpting patterns of neural activity related to incentive motivation.

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

54. Neuroinflammatory mediators and amphetamines: Beyond biogenic amines

Chair: Bryan Yamamoto

Presenters: Gary Gudelsky, James O'Callaghan, Nicole Northrop, Jesus Angulo

The substituted amphetamines, methamphetamine (METH) and MDMA, damage dopamine and serotonin terminals in addition to their abuse liability. The classical line of thinking is that this damage is the result of oxidative stress and excitotoxicity; however, there is emerging new evidence that neuroinflammatory mechanisms play a role. Moreover, it is becoming apparent that damage produced by these drugs extends to targets other than biogenic amine terminals. Gary Gudelsky will present new evidence that links glutamate with inflammatory processes and the novel finding that MDMA produces a loss of GABAergic cells in the hippocampus. He will show that MDMA increases cyclooxygenase (COX) activity in the hippocampus and that COX inhibition prevents increases in extracellular glutamate and the loss of GABAergic cells. James O'Callaghan will extend the involvement of neuroinflammation to the neurotoxic effects of METH. His new findings show that chronic corticosterone enhances and primes the inflammatory response to METH as indicated by the exacerbation of increases in toll-like receptor expression, LIF, CCL2 and IL-1B. By extension, Nicole Northrop will show that chronic stress exposure before METH produces a long-term leakage in the blood brain barrier (BBB) and a decrease in its tight junction proteins; the effects of which are blocked by COX inhibition after the exposure to METH. Her results indicate a breach of the BBB mediated by persistent neuroinflammation that occurs after but not during METH exposure. Jesus Angulo will link another inflammatory mediator, nitric oxide, to the effects of METH. He will present evidence of a differential modulation of NO by the striatal neuropeptides, substance P, NPY and somatostatin, which can influence striatal neuron damage in response to METH. Together, the panelists will lead a discussion on recently identified novel mediators, toxicities, and possible therapeutics associated with substituted amphetamine exposure.

55. Frontal cortical limbic circuits impact your thinking about drinking

Chair: Fulton Crews

Presenters: Fulton Crews, Theodora Duka, Dai Stephens, Olivier George

Addiction involves poor decision making and a lack of behavioral flexibility. Frontal cortical control matures during adolescence, a stage in life when experimentation with drugs is common. The frontal cortex is linked to limbic structures regulating impulsiveness, anxiety and affect. This panel will present human and animal studies investigating frontal cortical function and how it relates to alcohol and stress induced addiction-like behaviors. Fulton Crews (University of North Carolina) will present frontal cortical-limbic neurocircuitry and how it relates to adolescent maturation, comparing rodent and human studies. Binge drinking models that cause persistent alterations in frontal cortical, amygdala, nucleus accumbens, and hippocampal activity will be presented. Data on blunted adult frontal cortical activity and forebrain cholinergic signaling that increase limbic activation contributing to negative affect and blunted behavioral flexibility will be presented. Theodora Duka (University of Sussex) will present studies on human alcohol abusers relating increasingly dependence on alcohol to performance deficits in an incentive conflict task that is associated with compromised functional and structural integrity of prefrontal cortex, which may thus impair the ability to control future drinking. Dr. Dai Stephens (University of Sussex) will overview animal models for studying impulsive reward seeking in rodents, and the effects of both acute and long-term alcohol on impulsive behavior. Long-term effects mimic those seen in alcohol-dependent patients. Dr. Olivier George (Scripps) will present a hypothesis of how stress may interact with frontal cortex top-down control. Models of excessive alcohol consumption and extended access to self-administration of drugs of abuse will highlight the role neuroadaptation in brain stress systems as well as deficits in frontal cortex function in compulsive drug seeking.

56. Sex, drugs, and rocky road: Neurobehavioral similarities and differences between drug and nondrug reinforcers

Chair: Chris Olsen

Presenters: Lique Coolen, Marilyn Carroll, Paul Kenny, Peter Thanos

Compulsive engagement in behaviors such as sex, exercise, and eating has been likened to drug addiction. There is a high degree of overlap between brain regions involved in processing natural rewards and drugs of abuse, and recent evidence suggests that some of the neuroadaptations associated with exposure to drugs of abuse are also associated with exposure to nondrug reinforcers. The focus of this panel will be to discuss recent developments in our understanding of the neurobehavioral effects of exposure to drug and nondrug reinforcers and the implications this has to the field of addiction. Lique Coolen (University of Michigan) will show that experience with sexual behavior causes plasticity of ventral tegmental dopamine neurons and nucleus accumbens neurons, including changes in soma size, dendritic spines and up regulation of deltaFosB. She will also demonstrate that this sex reward-induced plasticity is associated with altered psychostimulant reward. Marilyn Carroll (University of Minnesota) will present data from rats bred for high (HiS) or low (LoS) sweet intake that demonstrate greater vulnerability to drug abuse in HiS rats, and these behavioral differences are accompanied by differences in neuronal activity in reward areas of the brain. Her data also suggest that these genetic differences may be due to differences in both reward reactivity and sensitivity to aversive events, and that similar differences have been found in rats selected for high and low impulsivity, novelty reactivity, wheel-running. Paul Kenny (Scripps Florida) will discuss new data demonstrating dissociable mechanisms for hypocretin (orexin) transmission in the regulation of drug versus food reward. Finally, Peter Thanos (Brookhaven National Laboratory) will outline several neuroimaging techniques and how they are integrated with other neuroscience methods to study drug and nondrug rewards in clinical and preclinical studies.

57. Disorders of cognitive function: From genes to mechanisms

Chair: Albert Galaburda

Presenters: Albert Galaburda, Daniel Geschwind, Daniel Weinberger, Allan Reiss

Genetic epidemiology has reached the point where the discovery of genes with main effects on disease is relatively easy, and the discovery of genes with more modest effects, which however interact with other genes and/or environments, more difficult but to a large extent doable. Next, advances in molecular biology and neuroscience are making it possible to identify developmental and functional molecular pathways that, when deviant, contribute importantly to the incidence of diseases and disorders affecting complex behaviors. Implemented in collaborative projects, these advances hold some promise for helping in the early identification and improved treatment of these conditions. The present panel will focus on five conditions, some quite common, that are yielding to the power of a new and powerful biological enterprise, implemented in different ways. The first talk will present results from genome-wide expression profiling that demonstrate that genes involved in autism are often highly co-regulated, forming groups called modules that show molecular convergence. The second talk will show that studies on the genetic risks for schizophrenia using the CBDB datasets, show significant epistasis (gene-gene interactions) for SNPs in COMT with other genes that putatively also impact on the tuning of cortical microcircuitry, including GAD1, GRM3, DAAO, RGS4, and DTNBP1, as well as other interactions. The third talk will present results from in utero RNAi and knockout experiments in rodents that illustrate the roles that dyslexic risk genes *Dyx1c1*, *Dcdc2*, and *Kiaa0319* have in neuronal migration and circuit formation. Finally, the last talk will compare two genetic syndromes, Fragile X and Williams Syndrome, which display contrasting social behavior vis a vis brain anatomical and functional measures.

58. Regulation of AMPA-type glutamate-receptor activity and localization

Chair: Andres Maricq

Presenters: Steven Tavalin, Richard Huganir, Andres Maricq

Basal synaptic transmission in the brain is largely mediated by AMPA receptors. Their precise postsynaptic localization is critical for fast and effective synaptic transmission. Their prevalence at postsynaptic sites is strictly regulated, with

permanent changes occurring during various forms of synaptic plasticity including LTP, LTD, and homeostatic mechanisms ensuring balanced excitatory input into individual neurons. Their dysfunction or dysregulation underlies many mental and neurological diseases including depression, autism, epilepsy, posttraumatic stress disorder, and drug addiction. Despite huge progress over the last two decades on the regulation of AMPAR activity and postsynaptic localization, much remains to be learned. This panel will focus on molecular mechanisms of the PKA-mediated regulation of AMPA receptors containing the GluA1 subunit under physiological and pathophysiological conditions. Steven Tavalin (University of Tennessee) will review the molecular organization of the A kinase anchor protein AKAP79/150 signaling complex, which orchestrates kinase/phosphatase-dependent regulation of GluA1. Richard Huganir (HHMI, Johns Hopkins University) will discuss the role of GluA1 regulation in fear conditioning and the erasure of fear memories. Andres Maricq (University of Utah) will talk about the transport of GLR-1-containing AMPA receptors in *C. elegans* by the microtubule-dependent motor Kinesin-1/UNC-116, and how transport contributes to synaptic transmission and behavior.

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

59. Opting for opsins: Problems and promises for manipulating neural circuits in vivo

Chair: Karen Gale

Presenters: Kay Tye, Luis DeLecea, Xue Han, Patrick Forcelli

Optogenetics has created a new frontier for studying neural substrates of behavior in animal models. This panel will critically evaluate the state of this new art and discuss clever ways to introduce and utilize opsin-coupled channels to photically activate or silence specific components of brain circuits in behaving animals. Emphasis will be on strategies for applying optogenetic tools to study functional neuroanatomy, behavior, and the etiology and treatment of various neurological disorders. Kay Tye will discuss experiments manipulating specific limbic system networks by optogenetically targeting defined projections in regions such as amygdala, and how this achieves behavioral outcomes that are distinct from what is seen by simply targeting particular cell types. She will also discuss new advances in the use of transgenic rats that allow for selective control of activity in ventral tegmental dopamine neurons. Luis de Lecea will describe the use of an array of cell-type specific promoters that allow the optogenetic manipulation of discrete populations of neurons in hypothalamus,

substantia innominata, and locus coeruleus, to dissect out causal interactions between defined substrates for the control of arousal, sleep, feeding, learning, and reward. He will discuss “combinatorial optogenetics”—where different combinations of distinct neuronal populations can be concurrently activated or silenced in an effort to analyze highly complex interactions governing behavior. Xue Han will discuss the use of optogenetics in controlling cortical excitatory neurons in monkeys, and the resulting modulation of neural circuit dynamics. She will also share recent efforts to improve the function and the use of opsins in both monkey and mouse models. Finally, Patrick Forcelli will discuss the prospects for using inhibitory and excitatory optogenetic manipulations to control epileptic seizures by amplifying seizure-resisting mechanisms in the rat basal ganglia.

Panel • Thursday, 7:30–9:30 AM • Superior B

60. Neuronal RNA regulation

Chair: Melissa Barker-Haliski

Presenters: Nora Perrone-Bizzozero, Scott Barbee, Miles Wilkinson, Jean-Claude Lacaille

To control the complex cellular signaling required of neurons, more than 400 mRNAs are trafficked from the nucleus and localized to activated synapses. Numerous cis-acting elements and trans-acting factors facilitate dendritic trafficking and local translation. The coordinated mRNA regulation and local protein synthesis can then facilitate both long-term potentiation and long-term depression. Thus, post-transcriptional RNA regulation provides a crucial means for neurons to respond to myriad external stimuli in a highly coordinated manner. This panel will provide an in-depth discussion of the complex cellular events that orchestrate mRNA trafficking and local protein synthesis to mediate changes in synaptic plasticity. Furthermore, dysfunction in these regulatory factors can contribute to aberrant synaptic plasticity and neurological disorders. To start the discussion, Dr. Nora Perrone-Bizzozero (U. of New Mexico) will demonstrate that brain-specific HuD RNA binding proteins interact directly with neuronal mRNAs to modulate synaptic plasticity. Dr. Scott Barbee (U. of Denver) will then describe how the spatial restriction of *Drosophila* dendritically localized mRNAs and localized protein synthesis tightly regulates the neuronal response. Dr. Miles Wilkinson (UCSD) will explain how the brain-specific microRNA-128 can suppress the Nonsense-Mediated Decay RNA surveillance pathway in developing neurons and how mutations in regulators of this pathway can lead to human neurological disorders. Finally, Dr. Jean-Claude

Lacaille (U. of Montréal) will describe how the RNA binding proteins, Staufen 1 and 2, can alter local protein synthesis-dependent long-term potentiation and long-term depression in rat hippocampal pyramidal cells. Taken together, this panel will provide a provocative discussion of the post-transcriptional regulatory events that allow thousands of synapse-specific responses transcribed from but a single neuron.

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

61. Epigenetics in human brain

Chair: Joel Kleinman

Presenters: Gustavo Turecki, Joel Kleinman, Rahul Bharadwaj, Carolina Montano

Epigenetic modifications are known to play a critical role in gene expression, chromosomal stability, and embryonic development, and have been documented in cancer and in neurological disorders. Relatively little is known about methylation signatures of the developing human brain and in neurodevelopmental brain disorders. We will provide data on epigenetic signatures from the human postmortem brain studies. Gustavo Turecki will show the results of genome-wide MeDIP-Seq study in brains of subjects who committed suicide and in controls. Joel Kleinman will present DNA methylation data from the postmortem human prefrontal cortex across the lifespan and show strong associations of methylation signatures with genotypes. Comparative analyses of disease cohorts reveal epigenetic dysregulation at hundreds of loci that are enriched for neurodevelopmental genes. Rahul Bharadwaj, using chromosome conformation capture (3C) assays in postmortem brain tissue and neuronal and non-neuronal cell cultures, will show reproducible three-dimensional chromatin architectures and loop formations extending across several hundred kilobases at loci encoding glutamate receptor and GABA synthesis genes. These chromatin architectures are cell-type-specific and closely associated with gene expression activity. Carolina Montano will report on DNA methylation profiles across human cerebral cortex, cerebellum, and hippocampus using comprehensive high-throughput arrays for relative methylation (CHARM) microarrays, which interrogate 6 million CpGs. Besides finding distinct methylation profiles for each brain region and assessing the contribution of neuronal versus glial methylation, she also identifies sex-specific methylation loci in the genome. This panel will present the molecular mechanisms that fine-tune and regulate changes in gene expression and neuronal function.

62. The role of drug-cue memories in relapse: 1 problem, 4 neurotransmitter systems

Chair: Ashley Fricks-Gleason

Presenters: Ashley Fricks-Gleason, Devin Mueller, Kathryn Cunningham, Kathryn Reissner

The abuse of illicit drugs is a global problem with significant impacts on our health care and criminal justice systems, as well as our economy. While initial drug use can be attributed to exploration or pleasure-seeking, long-term drug use appears to be maintained by memories of powerful rewarding effects of the drugs. The motivational influence of these memories is referred to as craving and can lead to relapse. The relapse of addicts into drug seeking is often triggered by discrete cues or contexts paired with drug exposure. Neutral cues previously paired with drug use take on incentive motivational properties that can lead to an intense craving by addicts. The molecular mechanisms and neurotransmitter systems underlying these drug-cue associations are a topic of active investigation. Increased understanding of these mechanisms will prove to be critical in the development of targeted therapeutics to aid in the treatment of relapse. This panel will focus on the role of four different neurotransmitter systems in the formation and maintenance of drug-cue memories. The panel will begin with Ashley Fricks-Gleason (University of Utah), who will provide background on the role of drug-cue memories in relapse and introduce a novel role for dopamine in the consolidation of extinction of cocaine-cue memories. Second, Devin Mueller (University of Wisconsin, Milwaukee) will describe recent evidence that retrieval of cocaine-associated memories is mediated by norepinephrine acting at central β -adrenergic receptors. Kathryn Cunningham (University of Texas Medical Branch) will then present work investigating the role of serotonin signaling in cocaine-seeking behavior. Finally, Kathryn Reissner (Medical University of South Carolina) will discuss the role of glutamate homeostasis in cocaine-seeking behavior, with emphasis on elucidation of specific components in the control of glutamate homeostasis most important to relapse.

63. Neuroethological approach to behavioral choice

Chair: Rhanor Gillette

Presenters: Todd Coleman, Björn Brembs, Michael Platt, Rhanor Gillette

Organism design centers around three functions: acquisition of resources, defense, and reproduction. Decisions for expression of the behaviors serving

these functions are determined by moment-to-moment integration of sensation, internal state, and memory into an assessment of costs, benefits, and risks. Thus, comparative studies of decision processes are unified by common bases in behavioral choice in simple and complex animals alike. Novel approaches to these principles are addressed here in conceptual engineering applications, in primate foraging, and in simple model systems. Todd Coleman reverse engineers an approach to neuroeconomic decision—inverse optimal control—to describe utility functions from behavioral observations and applies the framework to multi-agent team decision and the development of addictive behavior. The approach is broadly applicable to neuroethological problems. Björn Brembs deals with vital decisions to forage or mate, stay or go, and fight or flight in completely new situations, where outcome of any decision is not immediately predictable. Data are presented from *Drosophila* on initiation of spontaneous actions and evaluation of the resulting outcomes. Michael Platt addresses the neuronal basis of sequential foraging decisions in the macaque dorsal anterior cingulate cortex—an area linked to reward monitoring and executive control. He links the Marginal Value Theorem of behavioral ecology for optimal patch exploitation to neuronal activity. Finally, Rhanor Gillette illustrates simple circuitry and simulation for appetitive control of cost-benefit decision in a predatory sea-slug, then considers a bottom-up approach to evolution of complexity in brain and behavior.

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

64. Homeostatic Plasticity: Single synapses to neural circuits

Chair: Michael Sutton

Presenters: Jason Shepherd, Jessica Loweth, Jean-Claude Beique, Michael Sutton

A diverse array of plasticity mechanisms exist that can profoundly impact brain function in both adaptive and maladaptive ways. Homeostatic forms of synaptic plasticity, characterized by compensatory synaptic adaptations invoked by sustained changes in network and/or synaptic activity, are thought to be particularly important for promoting long-term stability in neural circuits. For many years, however, the molecular mechanisms, functional significance, and spatial scale of homeostatic control in the nervous system have been debated. This panel will discuss recent insights that bear on each of these issues, ranging from elucidating key molecular players, identifying new functional (or dysfunctional) roles of homeostatic plasticity in neural circuits, and novel insights into the nature and implications of local homeostatic capabilities at synapses. Jason Shepherd (MIT) will discuss both *in vitro* and *in vivo* studies that identify the immediate early gene *Arc/Arg3.1* as critical for establishing compensatory adaptations at synapses in the hippocampus and cerebral cortex. Jessica Loweth

(Rosalind Franklin University) will discuss how compensatory adaptations in the nucleus accumbens may link a particular form of homeostatic plasticity—synaptic scaling—with addiction. Jean-Claude Beique (University of Ottawa) will discuss recent insights made possible through the use of 2-photon glutamate uncaging and imaging, namely, that individual synapses are autonomous and independent homeostatic units. Since homeostatic control can be implemented on the single synapse scale, this raises the question of how these compensatory mechanisms co-exist with other forms of synaptic plasticity at those sites. Michael Sutton (University of Michigan) will present data examining how homeostatic plasticity mechanisms locally interact with Hebbian processes (e.g., LTP/LTD) important for information storage.

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

65. The neuroplasticity of chronic pain alters perception of reward

Chair: Carolyn Fairbanks

Presenters: Andrea Hohmann, Carrie Wade, Zaijie Wang, Carolyn Fairbanks

The increased use of sustained released opioids for chronic pain management has fostered a reconsideration of how reinforcing analgesics should be used as chronic medications. Reinforcing properties of analgesics have largely been studied in animal models in which chronic pain conditions are notably absent. However, the CNS undergoes neuroadaptive reorganization under chronic pain states. Therefore, assumptions regarding performance of analgesic agents derived from subjects with normal nociceptive signaling may not translate to subjects with established chronic pain. In recent years, principles from operant and classical conditioning have been applied to models of chronic pain states in order to advance our understanding of how analgesic reinforcing and nonreinforcing drugs perform under these neuroplastic conditions. This panel will present a series of studies evaluating reinforcing compounds across distinct models of chronic pain. In addition, analgesia, as a reinforcing phenomenon, will be discussed. Andrea Hohmann (Indiana University-Bloomington) will examine the impact of nerve injury on reinforcing properties of non-opioid (i.e., cannabinoid) and opioid analgesics in a model of neuropathic pain and discuss the impact of repeated analgesic treatment on the development and maintenance of neuropathic pain states produced by chemotherapeutic treatment. Carrie Wade (Scripps Research Institute) will present results comparing the performance of several clinical relevant opioid reinforcers in rodent models of chronic pain. Zaijie Jim Wang (University of Illinois Chicago) will present data

using the conditioned place preference model to demonstrate that analgesic states themselves can be reinforcing under conditions of chronic pain, independent of the properties of the specific analgesic applied. Carolyn Fairbanks (University of Minnesota) will summarize what is known regarding neuroanatomical changes that may contribute to the outcomes presented.

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

66. The immune system in CNS: Friend and foe?

Chair: Marcela Pekna

Presenters: Christine Ekdahl Clementson, Alexander Stephan, Lisa Boulanger, Michal Schwartz

Until recently, CNS was considered immune privileged and any immune response in CNS was therefore regarded as detrimental. However, based on accumulating evidence, this view has been dramatically changing. Innate as well as adaptive immune systems constantly interact with CNS, and this interaction is important for normal brain development and function, neuroprotection, and tissue repair. On the other hand, malfunctioning or excessive immune responses may lead to pathology where the destructive activity outweighs the benefits. Dysfunctional immune response in the CNS has been implicated in the pathogenesis of a range of conditions such as epilepsy, autism, schizophrenia, neurodegeneration, and impaired functional recovery after stroke and spinal cord injury. The actions of immune components can also change depending on the context, and there is ample evidence demonstrating their functions outside the traditional view of inflammation. This panel will discuss the multiple functions of immune cells and molecules in CNS development and normal maintenance, control of neurogenesis in health and disease, as well as the consequences of immune response malfunction for CNS pathologies. First, Christine Ekdahl Clementson (University of Lund, Sweden) will present the current view on the involvement of neuroinflammation and microglia in epilepsy. Alexander Stephan (Stanford University) will discuss the role of the complement system in synapse elimination during development and neurodegeneration. Lisa Boulanger (Princeton University) will present data on the functions of MHC class I in synaptic plasticity in the normal and diseased brain with emphasis on autism and schizophrenia. Finally, Michal Schwartz (The Weizmann Institute of Science, Rehovot, Israel) will discuss the concept of protective autoimmunity, the importance of macrophages and T cells for normal CNS function, and their role in recovery from acute and chronic neurodegenerative conditions.

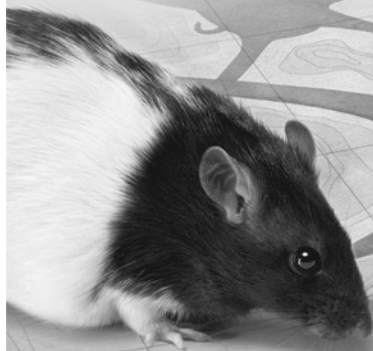
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Poster Abstracts

Sunday, January 22, 2012

P1 • The role of cortical dopamine 1 receptors in delayed discounting and its reversal with methylphenidate

Susan Andersen, Heather Brenhouse, Nadja Freund, Britta Thompson, Ka Sonntag*

Most humans, as well as rats, will choose a larger reward later over a smaller reward sooner. This paradigm of impulsive choice behavior is known as delayed discounting. A subset of individuals with ADHD is impaired in this task and is also at higher risk for substance use disorder than the normal population. Prepubertal treatment with the methylphenidate in rats reduces sensitivity to cocaine-associated environments. We have shown that the overexpression of the dopamine D1 receptor in prefrontal cortex projections to the nucleus accumbens core (pPFC \Rightarrow NAC) is associated with increased sensitivity to cocaine-associated environments. Here, we determined whether (1) delayed discounting is related to elevated D1 on glutamate neurons and (2) if methylphenidate reduces this behavior in adulthood by modulating this specific receptor population. A lentiviral vector that overexpressed D1 dopamine receptors specifically in glutamate neurons (e.g., CamKII α .D1) in the pPFC increased impulsive choices; CamKII α .D1 rats chose the smaller, immediate reward rather than waiting 5 sec for a reward that was four times larger. Normal control and CamKII α .GFP subjects waited for the larger reward after a delay of 5, 10, and 15 sec. A second set of experiments demonstrated that prepubertal methylphenidate treatment reduced impulsive choice in young adult rats by reducing the number of immunoreactive neurons for D1 for the PFC \Rightarrow NAC pathway. Together, these results support the hypothesis that prepubertal methylphenidate reduces impulsive choice and sensitivity to cocaine-associated environments by modulating D1 receptor expression on pPFC \Rightarrow NAC neurons.

P2 • Environmental enrichment: Differential effects of drugs on object recognition memory in rats

Arjan Blokland, Sven Akkerman, Jos Prickaerts*

Drug effects are usually evaluated in animals that are housed under standard conditions. However, it is assumed that rats raised in an enriched environment (EE) may be more comparable to the human condition, as compared to rats

raised in a standard laboratory condition. Therefore the validity of the use of standard-housed animals in drug research could be questioned. In the present study, we examined the effects of scopolamine and a PDE5 inhibitor on object recognition performance in standard-housed and EE rats. No differences were found in time-dependent forgetting (1- and 24-h) between both experimental groups. Also, scopolamine had similar effects in both standard-housed and EE rats at the doses tested (0.03-0.3 mg/kg). However, the PDE5 inhibitor did not improve memory performance in EE rats. These data suggest that although scopolamine was effective to impair memory performance, cognition enhancement was not found with a supposed cognition enhancer. These data question the use of standard-housed animals for the development of cognition enhancers in animal research.

P3 • Amyloid deposition is an immunosuppressive event

Carol Colton, Donna Wilcock, Jennifer Lee, Michael Vitek*

Our goal was to more fully characterize the inflammatory response in APP transgenic mice with and without disease progression, to better understand the relationship of immune state to amyloid pathology. Quantitative RT-PCR and protein analyses were used to measure pro-inflammatory, anti-inflammatory, and repair factors in mice expressing mutated human APP that show amyloid deposition alone (APP) or amyloid-mediated disease progression (APP/NOS2-/-). Immune activation was followed from earliest pathology at 6 weeks to 52 weeks of age where abundant amyloid, tau pathology and neuronal loss were evident. In mice that express amyloid only and at the earliest observation of amyloid pathology in mice that show disease progression, we find increased expression of alternative activation genes with little to no expression of classical activation (pro-inflammatory) genes. Disease progression in the APPSwDI/mNOS2-/- mice is associated with increasing expression of IL-1b and later, by increased TNFa. These changes in pro-inflammatory cytokines are associated with increasing tau and neuronal pathology. However, the increase is matched in time with increased expression of IL-1Ra and TGFb; anti-inflammatory factors that oppose IL-1b and TNF actions. C1Q and cystatin protein levels rise late when neuronal loss is most evident. Overall, we suggest that amyloid deposition results in a strong polarization of the inflammatory response to an immunosuppressive state. When amyloid is present alone, little classical inflammation is present. When disease progression occurs as in the APPSwDI/NOS2-/- mice to now show tau pathology and neuron loss, a restrained classical inflammatory response plus retention of alternative activation and acquired deactivation is observed.

P4 • Spreading convulsions, spreading depolarization, and epileptogenesis in human cerebral cortex

Jens Dreier, Jed Hartings*

Objectives: Spreading depolarization (SD) is characterized by a large direct current (DC)-shift. Near-complete sustained depolarization above inactivation threshold for action potential (AP) generating channels initiates spreading depression of brain activity [1]. By contrast, epileptic seizures show modest sustained depolarization below inactivation threshold for AP-generating channels. This allows synchronous, frequent neuronal firing. Nevertheless, Leão described in animals that silencing of brain activity induced by SD changed during electrical stimulations. Eventually, epileptic field potentials were recorded during the period which had originally seen depression of activity.

Methods/Results: We here report on such spreading convulsions in 2 of 25 consecutive aneurismal subarachnoid hemorrhage (aSAH) patients in vivo using subdural electrocorticography (ECoG). Moreover, twenty-one of 25 aSAH patients (84 %) had 656 SDs, in contrast to only three patients (12 %) with 55 ictal epileptic events isolated from SDs. SD frequency and depression periods per 24-hour recording episodes showed an early and a delayed peak on day 7. Patients surviving aSAH with poor outcome at 6 months showed significantly higher total and peak numbers of SDs and significantly longer total and peak depression periods during the ECoG monitoring than patients with good outcome. Three years after aSAH, 44 % of survivors had developed late post-hemorrhagic seizures. In those, peak SD number had been significantly higher (15.1 [11.4, 30.8] versus 7.0 [0.8, 11.2] events per day, $P = 0.045$). *Conclusion:* Monopolar recordings here provided unequivocal evidence of spreading convulsions in patients. Hence, practically all major pathological cortical network events in animals have now been observed in people. Moreover, early SDs may indicate a risk for late post-injury epilepsy.

P5 • The role of neuronal nitric oxide synthase-containing striatal interneurons in methamphetamine-induced dopamine neurotoxicity

Ashley Fricks-Gleason, Danielle Friend, Kristen Keefe*

It is well established that exposure to multiple high doses of methamphetamine (METH) produces damage to central monoamine systems. A number of factors, including the production of nitric oxide (NO), have been implicated in this neurotoxicity. While it is relatively clear that NO contributes to METH-

induced neurotoxicity to the DA nerve terminal, the source of this NO has not been clearly delineated. There is considerable evidence suggesting that the generation of NO arises a consequence of the activation of neuronal nitric oxide synthase (nNOS). For example, a neurotoxic regimen of METH fails to induce striatal DA loss in mice with targeted deletion of nNOS. Unfortunately, this blockade of toxicity is confounded by the fact that the mice thus treated do not show the METH-induced hyperthermia known to critically contribute to METH-induced neurotoxicity. However, pretreatment of mice with nNOS inhibitors does not attenuate METH-induced hyperthermia but does prevent the METH-induced toxicity to DA neurons. In striatum, nNOS is located postsynaptic to the DA nerve terminal in a subpopulation of striatal interneurons. Thus, we hypothesize that DA-mediated activation of the nNOS-containing striatal interneurons is necessary for METH-induced neurotoxicity. These interneurons, along with the cholinergic neurons of striatum, selectively express the neurokinin-1 (NK-1) receptor, which is activated by the neuropeptide Substance P. Consequently, toxins targeted to NK-1 receptor-containing neurons can be used to lesion this population of striatal interneurons. One such toxin, a conjugate of Substance P to the ribosome inactivating protein saporin (SSP-SAP), has been shown to be effective in selectively destroying neurons expressing the NK-1 receptor in striatum. Therefore, using targeted deletion of the nNOS-containing interneurons via SSP-SAP, we are examining the extent to which impairing post-synaptic production of NO attenuates METH-induced neurotoxicity.

P6 • Characterization of neurons in the prefrontal cortex activated during persistent heroin craving in rats

Evan Goldart, Bruce Hope, Yavin Shaham, Sanya Fanous*

Cue-induced heroin seeking persists long after withdrawal from the drug. We have previously found that persistent cue-induced heroin craving is associated with increased activation of sparsely distributed neurons in the medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC). We hypothesize that these neurons play a role in cue-induced heroin craving. In this study, we used the neural activity marker Fos to identify and characterize prefrontal cortex neurons activated during an extinction test after prolonged drug withdrawal. Male Sprague-Dawley rats were trained to self-administer heroin (6-h/day; 0.075 mg/kg/infusion; infusions were paired with a light cue) and tested for cue-induced heroin seeking in a 90-min extinction test after 2 weeks of abstinence. Brains were then processed for fluorescent immunohistochemistry using the neuronal activity marker Fos and either NeuN, which marks all neurons, CamKII, which marks glutamatergic projection neurons, GAD, which marks GABA-

containing neurons, or neuropeptide Y (NPY), which is present in a subset of GABA neurons. Of all mPFC and OFC neurons, only 9% were Fos-positive. We found that 43-54% of these Fos-positive neurons were CamKII-positive, while 10-18% of the Fos-positive neurons were GAD-positive, and 7.5 % of Fos-positive neurons were NPY-positive. Since all NPY neurons in these brain areas are known to be GAD-positive, the latter data indicate that more than half of the activated GABA neurons were NPY-positive. Overall, extinction testing activates a sparsely distributed minority of neurons in mPFC and OFC comprised of different cell types. We are now using the Daun02 inactivation procedure to assess whether these neurons play a causal role in heroin-seeking behavior.

P7 • Amelioration of motor neuron degeneration in cellular and animal models of amyotrophic lateral sclerosis by exendin-4

Nigel Greig, Harold Holloway, Yazhou Li, Srinu Chigurupati, Mohammad Mughal, Mark Mattson, Brandon Harvey, Balmiki Ray, Debomoy Lahiri*

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease characterized by a progressive loss of motor neurons in the brain and, in particular, spinal cord. The incretin hormone, glucagon-like peptide-1 (GLP-1), facilitates insulin signaling, and the long-acting GLP-1 receptor agonist, exendin-4 (Ex-4), is currently used as an antidiabetic drug. GLP-1 receptors are widely expressed in the brain and spinal cord, and our prior studies have shown that Ex-4 is neuroprotective in several neurodegenerative disease rodent models, including stroke, Parkinson's disease, and Alzheimer's disease. Here, we characterized the neuroprotective actions of Ex-4 in both cell culture (NSC-19 neuroblastoma cells) and in vivo models (SOD1 (G93A) mouse) of ALS. Ex-4 proved to be neurotrophic in NSC-19 cells, elevating choline acetyltransferase (ChAT) activity and protecting cells from hydrogen peroxide-induced oxidative stress and staurosporine-induced apoptosis. Additionally, in both wild-type SOD1 and mutant SOD1 (G37R) stably transfected NSC-19 cell lines, Ex-4 protected against trophic factor withdrawal-induced toxicity. To assess in vivo translation, SOD1 (G93A) mice were administered vehicle or Ex-4 treatment at 6 weeks of age onwards to end-stage disease via subcutaneous osmotic pump to provide steady-state infusion. ALS mice treated with Ex-4 showed improved glucose tolerance and normalization of behavior, as assessed by running wheel, compared to control ALS mice. Furthermore, Ex-4 treatment attenuated neuronal cell death in the lumbar spinal cord; with immunohistochemical analysis demonstrating the rescue of neuronal markers, such as ChAT, associated with motor neurons. Together, our results suggest that GLP-1 receptor agonists may have therapeutic potential in ALS.

P8 • Dopaminergic modulation of cortical-striate circuits during positive and negative expectations

Henry Holcomb, Jacqueline Griego, Jef West, Stephanie Coates, Laura Rowland, Lynn Oswald*

Dopamine modulates interactions between multiple brain regions during affective and cognitive behaviors. It is unclear to what extent dopamine modulates interactions during positive expectation to the same extent it operates on negative expectations. This pilot study of six healthy volunteers used functional magnetic resonance imaging to characterize the interactions of cortical, striatal and thalamic regions. These same volunteers participated in amphetamine-induced dopamine release positron emission tomography raclopride studies. Measures of dopamine release from the ventral striatum were applied to a model that provided an estimate of interactions within a circuit under positive and negative expectation conditions. Mediation analysis shows that dopamine modulates the functional connectivity more extensively under negative expectation than positive. The ROI circuitry, consisting of insula, aCC, caudate, and thalamus, shows qualitatively more functional connectivity during Negative Expectation than Positive Expectation. Additionally, the Positive Expectation and Negative Expectation activations for the aCC, thalamus, and caudate are highly related ($r = 0.935; 0.903; 0.843$, respectively). This indicates similar actions in the two conditions. The difference between conditions in circuit function may be due to dopamine modulation of the functional connectivity between regions. PET measures of amphetamine-induced dopamine release in the ventral striatum (VS_DR) suggest circuit modulation in the cognitive/neural environment of Positive Expectation. VS_DR is predictive of insula, aCC, caudate, and marginally ($p = 0.070$) thalamus activations. This was the same for Negative Expectation: VS_DR was predictive of insula, aCC, caudate, and marginally ($p = 0.068$) the thalamus. This model is consistent with a modulating role for dopamine that reflects emotional salience. In this case a negative expectation may provide greater affective relevance than the positive.

P9 • Endogenous modulation of GABA(A) receptor function governs pathological sleepiness in the primary hypersomnias

Andrew Jenkins, Donald Bliwise, Kathy Parker, Lynn Marie Trotti, Paul Garcia, Mike Owens, James Ritchie, David Rye*

Sleep and sedation can both be induced by chemically enhancing the function of GABA(A) receptors. However, other than neurosteroids, it is not known whether the nervous system produces endogenous regulators of GABA(A)

receptors that interact with the anesthetic and benzodiazepine binding sites of the protein to control wakefulness. In this study, we isolated CSF from 31 hypersomnic patients. Using whole-cell patch clamped HEK cells expressing recombinant receptors, we found that GABA(A) receptor function was enhanced by hypersomnic CSF ($88.2\% \pm 45.2$ (s.d.) vs $35.8\% \pm 7.5$ (s.d.) for controls, $t = 6.28$, $p < 0.00001$; no effect was observed with CSF alone). Enhancement was greater for $\alpha 2$ versus $\alpha 1$, and negligible for $\alpha 4$ subunit containing receptors. Affected CSFs also modestly enhanced benzodiazepine (BZD)-insensitive GABA(A) receptors and did not competitively displace BZDs from human brain tissue. Flumazenil—generally believed to act as a competitive benzodiazepine antagonist—reversed these in vitro enhancements. In seven out of seven patients investigated, flumazenil, known to lack intrinsic in vivo activity, reversed the symptoms of sleepiness and restored normal vigilance. Therefore, we have found that a naturally occurring substance in CSF augments inhibitory GABA signaling and reveals a novel pathophysiology to extreme sleepiness that is readily reversed by a commonly available therapeutic.

P10 • Chronic L-DOPA treatment restores impaired basal ganglia gene expression in rats with methamphetamine-induced neurotoxicity

Kristen Keefe, Katharina Oldenburger, Elissa Pastuzyn, Melissa Barker-Haliski*

Methamphetamine (METH) is neurotoxic to central monoamine systems in humans and animals. Prior work from our laboratory has shown that the partial loss of dopamine (DA) in striatum of rats treated with METH leads to long-lasting changes in striatal gene expression, particularly in striatonigral efferent neurons, changes in basal ganglia-mediate learning and memory functions and impaired phasic DA transmission. We therefore are examining whether treatment with L-DOPA can restore altered striatal gene expression induced by METH. Male Sprague-Dawley rats received either 4 x 10 mg/kg (\pm) METH or saline, as a vehicle, at 2-hr intervals. In our design, we injected the subjects daily for three weeks with either saline or L-DOPA (50 mg, s.c.) 20 min after an injection of the peripheral decarboxylase inhibitor, benserazide. Densitometric analysis of film autoradiograms for preprotachykinin (PPT) mRNA expression in the dorsomedial and dorsolateral striatum revealed significant main effects of region ($p < 0.0001$) and pretreatment ($p = 0.03$), consistent with prior results showing greater PPT mRNA expression in lateral striatum and decreased expression in METH-pretreated rats. Furthermore, there was a significant region x pretreatment x L-DOPA treatment interaction ($p = 0.03$). Post-hoc analyses indicate that administration of 50 mg/kg L-DOPA increased PPT mRNA expression in the METH-, but not the saline-, pretreated rats, such that PPT mRNA expression was no longer different in the METH-pretreated rats

given L-DOPA relative to saline-pretreated rats given vehicle chronically for 3 weeks. These data suggest that administration of L-DOPA can restore striatal function in the context of METH-induced partial DA loss and, therefore, may be useful for managing deficits in basal ganglia-mediated cognitive functions observed in the context of METH-induced neurotoxicity. (Supported by DA024036.)

P11 • Mechanosensation, TRP channels, and calcium signaling in glaucoma

David Krizaj, Daniel Ryskamp*

Retinal cells are immersed within a mechanically active environment in which they must constantly cope with and adapt to hydrostatic pressure and osmotic stress. Mechanical stimuli such as increases in blood pressure and intraocular pressure (IOP) represent a key risk factor for developing glaucoma, a severe blinding disease in which retinal ganglion cells (RGCs) degenerate and die. The transduction mechanism through which increased IOP induces RGC death has remained a major unsolved puzzle in retinal research. Here, we sought to establish the role of mechanosensation in light-evoked signaling and pathophysiology of RGCs. We found that the mouse retina expresses mechanosensitive K⁺ and Ca²⁺-permeable TRAAK, TWIK, TREK, TRPC, piezo, and TRPV ion channels. TRPV4 was the most prominently expressed isoform. Its mRNA and protein were confined to RGCs with expression concentrated at the optic nerve head and the prelaminar optic region, which are primarily targeted by elevated IOP in glaucoma. Membrane stretch, temperature (37°C), or exposure to selective TRPV4 agonists elevated [Ca²⁺]_{RGC} in a Ruthenium Red- and Gd³⁺-sensitive manner. Responses to TRPV4 agonists were occluded by membrane stretch, revealing a nonredundant function in RGC mechanosensation. Multielectrode array recordings showed that TRPV4 activation induces >100-fold increase in the frequency of spontaneous RGC firing. Intriguingly, sustained TRPV4 stimulation induced apoptosis of RGCs but not photoreceptors, bipolar, or amacrine neurons. TRPV4 expression and localization were strongly affected in a chronic mouse glaucoma model. These results show that the specific subset of mouse retinal neurons is intrinsically mechanosensitive due to selective expression of TRPV4. Calcium influx, gated by TRPV4, regulates the excitability of healthy RGCs whereas excessive stimulation initiates neurodegenerative changes in RGCs that culminate in cell death, representing a plausible mechanism for glaucoma.

P12 • Phosphatase involvement in recovery from morphine desensitization in locus coeruleus neurons from morphine-tolerant rats

Erica Levitt, John Williams*

Tolerance to morphine-mediated G protein-coupled inwardly rectifying potassium conductance was observed in locus coeruleus neurons from rats treated with morphine for 6–7 days. This tolerance was long lasting since brain slices were washed in morphine-free buffer for several hours prior to testing. However, additional desensitization was observed when slices from morphine-treated rats were maintained in morphine. The concentration of morphine required to maintain desensitization was similar to the circulating concentration of morphine (1 μM), and incubation with 10-fold less morphine (100 nM) was insufficient. The desensitization was transient and recovered over 60 minutes of morphine washout. The time course of recovery was unaltered by the presence of the serine/threonine phosphatase inhibitor okadaic acid. However, the phosphatase inhibitor calyculin A, which more potently inhibits protein phosphatase 1 (PP1), delayed the recovery from morphine desensitization in slices from morphine-treated rats. In contrast, neither okadaic acid nor calyculin A affected the tolerance observed after a long-term (> 2 h) wash. These results identify two forms of tolerance induced *in vivo* distinguished by the time course of recovery and implicate PP1 activity during the recovery from transient desensitization. (Supported by T32NS007381 and DA08163.)

P13 • Alterations in mTOR pathway signaling following status epilepticus in immature vs. mature rats

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

Chemoconvulsants such as pilocarpine are used to induce episodes of prolonged continuous seizure activity (status epilepticus, SE). In adult rats, this initial insult leads to the generation of unprovoked seizures (epilepsy). A similar insult in immature rats does not lead to spontaneous seizures later in life; however, the insult does result in long-lasting cellular and molecular changes that alter hippocampal plasticity in adulthood. While the effects of SE on mTOR signaling in the adult brain have been widely studied, relatively less is known about the effects of SE on mTOR signaling in the immature brain. We examined hippocampal mTOR pathway activation through the phosphorylation (P) of the downstream molecules ribosomal S6 protein, eukaryotic initiation factor binding protein 1 (4EBP1), and AKT, in developing and adult

rats following pilocarpine-induced SE compared to age-matched shams. We performed a time course of mTOR activation over development to guide our choice of time points for the SE experiments. Western blotting revealed a significant decrease in hippocampal levels of P-S6, P-4EBP1 and P-AKT over postnatal development. However, at postnatal day (PD) 10, these levels remained significantly elevated compared with PD35 and adult (>6 months) (P14 days) increase in the levels of P-S6 and P-4EBP1, and a transient decrease in P-AKT (3 days) (n=5-8). In conclusion, the effects of SE on mTOR activation are different in immature vs. mature hippocampus. While additional investigations are necessary to further characterize this effect, our findings may have implications for therapeutics in epilepsy.

P14 • Mouse model of L-DOPA-induced nigrostriatal neurodegeneration

Eugene Mosharov, Haung Yu, Sarah Woodworth, Bryce Vissel, David Sulzer*

Parkinson's disease (PD) is a neurodegenerative disorder that may be caused by genetic and environmental factors. In our previous studies, we demonstrated that in cultured mouse dopaminergic neurons cell death can be induced by the combination of elevated cytosolic DA and the presence of alpha-synuclein. Additionally, cytoplasmic Ca²⁺ plays an important role of a "master switch" that upregulates DA synthesis, thereby making cells more susceptible to neurodegeneration. To investigate whether neurodegeneration *in vivo* can also be induced by the combined action of high cytosolic DA and alpha-synuclein, we chronically treated transgenic mice that overexpress alpha-synuclein under the control of TH promoter with DA precursor L-DOPA. Following 6 months of treatment, these mice displayed impaired performance on rotarod, beam walk, and hanging reflex tests compared to both untreated transgenic mice and non-transgenic animals treated with L-DOPA. Interestingly, animals performed significantly better at rotarod if they were trained before the start of the L-DOPA treatment compared to mice that received rotarod training only at the end of the treatment. Stereological assessment of the number of the number of SNpc neurons showed reduced DA neuronal counts, although the difference did not reach statistical significance. On the other hand, we found ~50% reduction in the density of DAT-positive fibers in the striatum of transgenic mice treated with L-DOPA. Taken together, behavioral, immunohistochemical, and biochemical data strongly support the synergistic effect of alpha-synuclein and cytosolic DA on neurotoxicity and provides a new mouse model of PD.

P15 • Investigating the dopamine D2 receptor (D2R) orthosteric binding site with analogues of sumanirole

Amy Newman, Mu-Fa Zou, Sameer Khatri, Rebecca A. Roof, Mayukh Chakrabarti, Robert Johnson, Prashant Dothamsetti, Lei Shi, Jonathan A. Javitch, Aaron Janowsky, Robert Luedtke, David R. Sibley*

Recently, the dopamine D3 receptor (D3R) protein was crystallized with the D2R/D3R antagonist eticlopride (Chien et al. 2010). Based on the high-resolution structural information, our comparative molecular modeling and simulations of D2R/D3R provided clues to designing novel and D2R selective ligands as pharmacological tools. To this end, we have chosen the putative D2R-selective agonist (McCall et al. 2005) sumanirole as a template for modification and have designed and synthesized a series of analogues in which modifications were made to the (1) 5-position secondary amine, (2) 8-position, and (3) bridgehead amide nitrogen. We discovered that sumanirole did not bind selectively to D2R, as reported, and has low affinity in our binding assays (D2R K_i = 1.4 μ M; D3R K_i = 1.2 μ M). Further, none of these compounds demonstrate D2R-selectivity using a beta-arrestin interaction functional assay. As beta-arrestin may lead to non-G-protein-mediated responses, it could be argued that our analogues are functionally selective and thus may not be effective in this assay. Therefore, we selected sumanirole and the five most potent analogues for further evaluation in the Go-BRET and mitogenesis functional assays. Preliminary data show that sumanirole was not a particularly D2R-selective agonist, nor were any of the analogues. However, we have discovered two D2R/D3R antagonists from this series (MFZ 13-16 and 13-19), demonstrating that we can convert an agonist into an antagonist with substitution at the amide nitrogen. To our knowledge, this is the first series of sumanirole-based molecules with this substitution pattern and provides an opportunity for both novel chemistry and drug design. Moreover, it is anticipated that these molecules will help further elucidate structural components of the D2R orthosteric binding site.

P16 • Cerebral blood flow response to functional activation

Olaf B. Paulson, Steen G. Hasselbalch, Egill Rostrup, Gitte Moos Knudsen, Dale Pelligrino*

Cerebral blood flow (CBF) and cerebral metabolic rate are normally coupled; i.e., an increase in metabolic demand will lead to an increase in flow. However, during functional activation, CBF and glucose metabolism remain coupled as they increase in proportion, whereas oxygen metabolism only increases to a minor degree—the so-called uncoupling of CBF and oxidative metabolism. Several studies have dealt with these issues, and theories have been forwarded

regarding the underlying mechanisms. Some reports have speculated about the existence of a potentially deficient oxygen supply to the tissue most distant from the capillaries, whereas other studies point to a shift toward a higher degree of non-oxidative glucose consumption during activation. In the present review, we argue that the key mechanism responsible for the regional CBF (rCBF) increase during functional activation is a tight coupling between rCBF and glucose metabolism. We assert that uncoupling of rCBF and oxidative metabolism is a consequence of a less pronounced increase in oxygen consumption. Based on previous studies, we take into consideration the functional recruitment of capillaries and attempt to accommodate the cerebral tissue's increased demand for glucose supply during neural activation with recent evidence supporting a key role for astrocytes in rCBF regulation.

P17 • Quantification and involvement of soluble GDNF receptor, GFR α -1, in dopamine regulation

Brandon Prueff, Michael Salvatore*

We have previously reported that age-related bradykinesia is associated with dopamine (DA) loss only in the substantia nigra (SN). Furthermore, over the lifetime, nigral DA correlates with locomotor activity, indicating that nigral DA can influence locomotor capabilities. We found that nigral DA loss was accompanied by a reduced capacity for DA biosynthesis, as indicated by decreased tyrosine hydroxylase (TH) protein and phosphorylation at ser31. Since glial cell line-derived neurotrophic factor (GDNF)-mediated signaling through GDNF family receptor α -1 (GFR α -1) can affect DA regulation, we investigated age-related changes therein, with a focus on GFR α -1 levels, which had yet to be characterized with respect to aging. GFR α -1 exists as both a glycosylphosphatidylinositol (GPI)-linked cell surface receptor and as a cleaved and soluble receptor. Soluble GFR α -1 in the SN positively correlated with TH and DA levels and was selectively reduced by ~30% with aging. Next, using a soluble GFR α -1 standard, we found that total tissue recovery of soluble GFR α -1 in the SN was ~3 ng indicating a probable loss of ~1 ng with aging. To further determine the role of soluble GFR α -1 in DA regulation, we unilaterally infused 1 and 2 ng soluble GFR α -1 into the SN of rats along with vehicle infusions into the contralateral SN. Infusion of soluble GFR α -1 tended to have a normalizing effect such that when nigral DA levels in the vehicle-infused hemisphere were either higher or lower than average, nigral DA levels in the GFR α -1-infused hemisphere were reduced or increased to average levels, respectively. This alteration in DA levels was matched by similar changes in TH. Thus, while exogenous soluble GFR α -1 can improve DA tone when levels are below average, it appears to engage a secondary compensatory mechanism to prevent further increases in DA if levels are above average. This serves as further evidence of the autoregulatory nature of the DAergic cell bodies in the SN.

P18 • High-throughput screening for allosteric modulators of the D2 dopamine receptor

David Sibley, Benjamin Free, Noel Southall, Trevor Doyle, Rebecca Roof, Jennie Conroy, Yang Han, Jonathan Javitch, Marc Ferrer*

The D2 dopamine receptor (DAR) is central in the etiology and/or therapy of many neuropsychiatric disorders; however, truly specific drugs for this receptor have been difficult to obtain. A novel pathway towards receptor-selective ligands is to identify allosteric modulators that bind to less conserved sites on the receptor and have the potential to be exquisitely selective. Allosteric modulators can exhibit a variety of functional activities, including positive or negative modulation of ligand interactions at the orthosteric site, modulation of agonist efficacy, including engendering functional selectivity, or they can exhibit agonist efficacy on their own. In order to identify allosteric modulators of the D2 DAR, we screened a 370,000 small molecule library to identify agonists (allosteric or orthosteric), positive allosteric modulators, or antagonists (allosteric or orthosteric). From this primary screen, 2,288 compounds with agonist activity, 1,408 compounds with potentiator activity, and 2,294 compounds with antagonist activity were cherry-picked. Upon further evaluation, none of the potentiators confirmed, while 650 agonists and 858 antagonists did not confirm. The remaining confirmed agonist and antagonist ligands were subjected to orthogonal and counter-screening functional assays. On the basis of these analyses, 745 agonist and 499 antagonist compounds were evaluated, using radioligand competition binding assays as a filter to separate orthosteric and allosteric ligands. These experiments resulted in the identification of 47 agonists and 48 antagonists that had insignificant effects on radioligand binding when tested using up to 40 μM of library compound. Many of these compounds exhibited their maximal functional effects (either agonist or antagonist activities) at concentrations that had no effect on radioligand binding to the orthosteric site. These compounds would thus appear to be allosteric agonists and negative allosteric modulators of the D2 DAR.

P19 • Both DGL α and DGL β regulate the production of 2-Arachidonoyl glycerol in autaptic hippocampal neurons

Alex Straiker, Tarun Jain, Jim Wager-Miller, Ken Mackie*

Cannabinoids are part of an endogenous signaling system consisting of cannabinoid receptors and endogenous cannabinoids (eCBs), as well as the enzymatic machinery to produce and break down these eCBs. Depolarization-induced suppression of excitation (DSE) is a form of cannabinoid CB1 receptor-mediated inhibition of synaptic transmission that involves the production of the eCB

2-arachidonoyl glycerol (2-AG). The role of diacylglycerol lipase (DGL) in the formation of 2-AG during depolarization is controversial: hippocampal DSI is absent in DGL α knockout mice, yet DGL inhibitors do not always block DSI. Furthermore, the two isoforms of DGL—DGL α and DGL β —are impossible to distinguish by available pharmacological tools. DGL α has received considerable attention in 2-AG production; what role, if any, may be played by DGL β remains largely unexplored. To investigate the roles of DGL α and DGL β in 2-AG production in DSE, we developed siRNA constructs for each enzyme. We found that our constructs reduced expression of these proteins by 70% and 72% in DGL α - and DGL β -expressing HEK293 cells, respectively. We then used these constructs to knock down DGL expression in autaptic hippocampal neurons. We find that knockdown of DGL α results in a substantial reduction of DSE, shifting the “depolarization response curve” from an EC50 value of 1.6 sec to 6.4 sec (nonoverlapping 95% confidence intervals). Interestingly, DGL β diminishes DSE as much or more (EC50 54.8 sec, nonoverlapping CI), suggesting that DGL β is responsible for a portion of 2-AG production in autaptic neurons. In separate experiments, we confirmed that siRNA for each DGL did not reduce the expression of the other DGL in HEK293 cells. We conclude that both DGL α and DGL β play a role in endogenous cannabinoid modulation of synaptic transmission. Our results identify DGL β as a new potential target for modulation of the cannabinoid signaling system.

P20 • Neuronal Pentraxin 1 regulates activity-dependent mitochondrial dynamics

Ramon Trullas, Joana Figueiro-Silva, Petar Podlesniy*

Neuronal activity regulates mitochondrial dynamics by modulating the balance between mitochondrial division and fusion, a process that determines the morphology of the mitochondrial network. In neurons, reduction of neuronal activity shifts this balance towards division (fission) and causes fragmentation of the mitochondrial network. Recently, it has become evident that pro- and anti-apoptotic members of the Bcl-2 family are involved in the regulation of the mitochondrial network. For example, BAX has a physiological role in regulating mitochondrial dynamics in healthy cells that is different from its pro-apoptotic function. A similar, but contrary, role has been reported for anti-apoptotic members of the Bcl-2 family of proteins such as BCL-xL. Nonetheless, the molecular mechanisms by which neuronal activity regulates mitochondrial dynamics are still not well characterized. We have investigated the role of Neuronal Pentraxin 1 (NP1) in the regulation of mitochondrial dynamics by

neuronal activity. We found that low neuronal activity induces the expression of NP1 that is targeted to mitochondria and that mitochondrial fragmentation caused by reduced neuronal activity requires NP1 expression. Moreover, our results indicate that NP1 contributes to mitochondrial fragmentation by facilitating the activation of BAX, which neutralizes, in turn, the positive effect that soluble BAX has on mitochondrial fusion. Overall, our results indicate that NP1 cooperates with BAX in the regulation of activity-dependent mitochondrial dynamics. (Supported by SAF2008-03514 from Ministerio Educación y Ciencia of Spain and CIBERNED.)

P21 • Nitric oxide-mediated regulation of β -Amyloid clearance via alterations of MMP-9/TIMP-1

David Wink, Lisa Ridnour, Ernie Brueggemann, Harry Hines, Michael Vitek, Carol Colton*

Removal of inducible nitric oxide synthase (NOS2) in 2 transgenic models of Alzheimer's disease (AD) promotes disease progression and AD pathology by linking increased amyloid plaques with neurofibrillary tangles and neuronal loss. Composed of 40–43 amino acid Amyloid- β peptides ($A\beta$), plaques are digested into less toxic products including $A\beta$ 1-16 by proteases including MMP-9, which along with its endogenous inhibitor TIMP-1 are regulated by nitric oxide (NO). We hypothesize that the role of NOS2-derived NO in AD pathology involves NO-mediated regulation of MMP-9 activity to facilitate plaque digestion and clearance. We developed an antibody that recognizes $A\beta$ 1-16, a specific MMP-9 digestion product, and used it to immunoprecipitate $A\beta$ 1-16 from brain tissue. Using mass spectrometry multi-reaction monitoring (MRM), we observed lower $A\beta$ 1-16 in brains from APPswDIxNOS2-/- animals when compared to APPswDI or APPswDIxNOS2-/-xTIMP1-/- animals. Using cell culture models, we show NO-mediated increases in MMP-9 proteolytic activity in conditioned media of microglia cells, which enhanced the degradation of fibrillar $A\beta$ added in vitro. This effect was abolished in cells that did not express MMP-9 enzyme. Together, these results suggest a role for NOS2/NO in the reduction of plaque burden, which involves enhanced plaque digestion and clearance that is mediated, at least in part, by increased MMP-9 activity and TIMP-1 suppression.

P22 • Transcription factor Nrf2 modulates microglia/macrophage-mediated phagocytosis and contributes to hematoma resolution after intracerebral hemorrhage

Jaroslaw Aronowski, Xiurong Zhao*

Hematoma components, especially erythrocytes (RBC) and the hemolysis products, deposited in brain parenchyma during intracerebral hemorrhage (ICH) induce secondary brain injury. Therefore, efficient cleanup of hematoma could be beneficial for inflammation resolution and functional recovery. Phagocytosis by microglia/macrophage (M/M Φ) represents an endogenous process underlying hematoma resolution. Nevertheless, oxidative stress generated by M/M Φ during phagocytosis may cause injury to M/M Φ themselves and inhibit the hematoma resolution process. Therefore, therapeutic strategy for optimal phagocytosis-mediated cleanup may require to be coupled to anti-oxidative approach. Our present study indicates that activation of transcription factor, nuclear factor-erythroid 2 p45-related factor 2 (Nrf2), with sulforaphane (SF) protects M/M Φ from "ICH-like" injury or oxidative stress *in vitro*. This effect of SF was linked to improved phagocytosis function, as SF-treated M/M in culture were more efficient in phagocytosis of RBC. M/M Φ treated with SF demonstrated (1) increase in the expression of Nrf2-regulated genes, including for the antioxidant/detoxifying proteins (catalase, SOD, NQO1, GST, HO-1, Hx) and scavenger receptor CD36; (2) reduced pro-inflammatory genes expression (TNF, IL-1); (3) reduced H₂O₂ in the MM Φ culture media, and (4) reduced neurotoxicity in the primary neuron-glia co-cultures. In agreement with the beneficial role of Nrf2, the Nrf2-deficient MM Φ were more susceptible to "ICH-like" injury and H₂O₂-mediated oxidative damage. Also, the phagocytosis was significantly inhibited by Nrf2 decoy and Nrf2 gene knockout (KO). Finally, in agreement with the key role of Nrf2, the Nrf2-KO mice subjected to ICH demonstrated delayed hematoma resolution and more severe brain edema. Thus, Nrf2 activation is beneficial to M/M Φ survival and phagocytosis function, and it may be a potential therapeutic target for improving hematoma and inflammation resolution after ICH.

P23 • Repeated amphetamine causes long-lasting plasticity at prefrontal cortical terminals within the nucleus accumbens core

Nigel Bamford, Ian Bamford, Wengang Wang*

Regulation of striatal activity by dopamine is required for behavioral reinforcement, but whether repeated treatment with the dopamine releaser amphetamine can provoke long-term changes in glutamate release from prefrontal cortical afferents to the nucleus accumbens core remains unclear, yet may be central to understanding the acquisition of drug dependency. Locomotor activity was monitored in male C57Bl6 mice (4–6 weeks), treated with amphetamine (2 mg/kg/d, 5 d) or saline. Evoked excitatory postsynaptic currents (eEPSCs), in response to paired cortical stimuli, and miniature EPSCs (mEPSCs; with TTX) were measured in medium spiny neurons from the accumbens core during withdrawal. In saline-treated mice, acute amphetamine (10 microM) depressed corticoaccumbal activity, as the amplitude of the first eEPSC decreased ($-16\pm 11\%$; $p=0.02$, paired t-test), while the paired-pulse ratio (PPR) increased ($19\pm 6\%$; $n=11$ cells; $p=0.02$) and the frequency of mEPSCs diminished ($-42\pm 13\%$; $n=12$; $p=0.03$). In amphetamine-sensitized mice, input-output curves showed a reduction in corticoaccumbal activity on withdrawal day (WD) 10, while acute amphetamine increased the eEPSC amplitude ($28\pm 10\%$; $p=0.04$), decreased the PPR ($-11\pm 6\%$; $n=8$; $p=0.04$) and increased the frequency of mEPSCs ($26\pm 8\%$; $n=7$; $p=0.01$), consistent with a paradoxical increase in synaptic activity following drug reinstatement. Similar results were also found on WD 21. Optical analysis using FM1-43 on WD 50 indicated a correlation between the increase in presynaptic release following drug reinstatement and the degree of locomotor sensitization in individual mice ($p=0.02$). Results suggest that repeated amphetamine can promote long-lasting, behaviorally-relevant plasticity in presynaptic activity that underscores the distinctive resistance of habit modification.

P24 • Grafting of neural stem cells to the hippocampus of young, irradiated mouse brains ameliorated behavior deficits

Klas Blomgren, Yoshiaki Sato, Niklas Karlsson, Changlian Zhu, Eva-Maria Öxler, Steffi Pfeifer, Noriko Shinjyo, Machiko Sato, Marie KL Nilsson, Marcela Pekna, H. Georg Kuhn, Carsten Culmsee*

Ionizing radiation persistently reduces the pool of neural stem and progenitor cells (NSPCs) in the dentate gyrus (DG) of the hippocampus, which may explain some of the learning deficits observed in patients treated with radiotherapy, particularly pediatric patients. A single dose of 8 Gy was administered

to the brains of postnatal day 9 (P9) C57BL/6J mice and 1.0×10^5 BrdU-labeled, syngenic NSPCs were injected into each hippocampus on P21, 12 days after irradiation (IR). Behavior was assessed 3 months later. IR impaired novelty-induced exploration, place learning, reversal learning, and sugar preference. IR also altered the movement pattern in the open field test. Grafting of NSPCs ameliorated, or even normalized, the deficits observed. Less than 4% of the grafted cells survived and could be found in the DG after 3 months. The IR-induced loss of endogenous, undifferentiated NSPCs in the DG was completely restored by grafted NSPCs in the dorsal, but not the ventral, blade. More than half of the grafted, surviving NSPCs differentiated into neurons or astrocytes, but neither could they replace the granule neurons that failed to develop due to IR (restoring GCL volume) nor did they exert appreciable effects on the endogenous NSPCs (increasing their numbers). The beneficial effects of grafted NSPCs are presumably mediated by trophic factors. Conditioned medium from the NSPCs was shown to protect hippocampal HT22 cells and cultured primary neurons from both growth factor deprivation-induced cell death as well as glutamate-induced cell death. These results point to novel strategies aimed at ameliorating the debilitating late effects of cranial radiotherapy, particularly in children.

P25 • Intermittent availability of alcohol does not necessarily lead to elevated drinking in mice

John Crabbe

Roy Wise (in 1973) and Selena Bartlett's group more recently have shown that intermittent exposure of rats to a 20% alcohol solution leads to higher alcohol intakes than continuous availability. Recently, Lara Hwa in Klaus Miczek's group reported dramatic, rapidly escalating drinking in C57BL/6J mice offered 20% alcohol vs water 3X/week. All these studies offered alcohol during 24 hr periods, either continuously or with chronic intermittent exposure (CIE). We tested high-preference C57BL/6J inbred mice and High Drinking in the Dark (HDID) mice, a line we have selectively bred to reach intoxicating blood ethanol levels after a short period of access to a single bottle of 20% alcohol. Male HDID mice offered a single bottle of 20% alcohol every other day during only a 4 hr access period failed to show greater intake than mice offered alcohol daily. Male C57BL/6J mice were offered 20% alcohol vs water in a two-bottle test during 4 hr or for 24 hr, either daily or MWF. There was a small increase in drinking with 24 hr CIE, but none with 4 hr CIE. An experiment with HDID mice modeled closely after the Hwa et al study showed a very modest elevation with 24 hr CIE exposure (this protocol offered a series of concentrations serially, building to 20% alcohol). We conclude that 4 hr of intermittent access

is insufficient to elevate drinking in mice. The lack of effect in HDID mice suggests that not all genotypes respond to intermittency. We do not know why we see much less escalation of drinking in C57BL/6J than Hwa et al. (Supported by the NIAAA [Integrative Neuroscience Initiative on Alcoholism [INIA-West] grant AA13519] and Center grant AA10760, and the US Department of Veterans Affairs.)

P26 • ETrA antagonist administered at various time points after TBI indicates time-dependent improvement in cerebral blood flow as measured by arterial spin labeling-MRI

Justin Graves, Anthony Kropinski, David Tiesma, Mike Kaufman, William Armstead, Donald Kuhn, Christian Kreipke*

ETrA antagonism administered at various time points after TBI indicates time-dependent improvement in cerebral blood flow as measured by arterial spin labeling-MRI. Traumatic brain injury (TBI) results in vasoconstriction which leads to hypoperfusion, cellular injury, and behavioral deficits. Our laboratories have shown that TBI-induced hypoperfusion can be ameliorated by intravenous administration of an endothelin receptor A (ETrA) antagonist. In this study, we used a rodent weight drop-acceleration impact model of diffuse brain injury to test the effects of a clinically relevant ETrA antagonist, Clazosentan, given at various time points and using a multiple injection paradigm, on cerebral blood flow (CBF) after TBI. Our results indicate that treatment with Clazosentan reduces the extent of TBI-induced hypoperfusion in a time-dependent manner. Furthermore, using a two-injection approach, we sought to determine the most efficacious manner for delivering Clazosentan. Our data show that the precise timing of delivery of drug is critical for the optimization of treatment and that a two-injection approach is more effective than single bolus treatment. Taken together, these results suggest that the “window of opportunity” for drug delivery is complex and great care will be needed as ETrA antagonism begins to be utilized in the clinical realm to mitigate the deleterious effects of TBI. (Supported by NIH NS064976, VARR&D RX000224.)

P27 • Dose-dependent effects of disulfiram on choices for cocaine over a monetary alternative in cocaine-dependent volunteers

Colin Haile, Richard De La Garza, James Mahoney, Thomas Kosten, Thomas Newton*

Background: Studies suggest that disulfiram (DS) may be an efficacious treatment for cocaine (COC) dependence, but results have not been consistent. To better understand DS's effects, we conducted a human laboratory study and

tested whether DS would alter choices for COC over a monetary alternative. *Methods:* Non-treatment seeking (N=17), COC-dependent volunteers participated in this randomized, placebo-controlled, within-subjects study. The study design had two phases, separated by a washout period of at least two weeks. In one phase, volunteers were treated with placebo; and in the other, they were treated with DS (250 mg/day). On the third day of treatment, participants were given ten opportunities to choose between receiving an infusion of saline (SAL) or COC (20 mg, IV) and a monetary alternative of increasing value that increased from 0.05 to \$16 over 10 choices. *Results:* Contrary to expectations, DS treatment significantly increased both the number of COC ($P<0.001$) and SAL infusion choices over money ($P<0.05$), and these effects of DS treatment were dose dependent. The number of COC infusion choices negatively correlated with DS dose when expressed as 250mg/kg for each participant ($r=-0.547$, $P=0.023$). DS treatment also significantly increased heart rate (P 's=0.02-0.10) and systolic blood pressure (P 's=0.009-0.10) over ten COC infusion choices. Participant weight correlated with systolic blood pressure response to an initial COC infusion in those treated with DS ($r=0.600$, $P=0.0182$). *Conclusions:* Low doses of DS relative to body weight increased the reinforcing effects of COC, whereas higher doses of DS reduced the reinforcing effects of COC. Results suggest that the impact of DS treatment on the reinforcing effects of COC is dose-dependent. These data may also explain variability in DS's efficacy seen in some clinical trials. Future research must take weight into account when selecting the appropriate DS treatment dose.

P28 • HDAC6 regulates GR signaling in serotonin pathways with critical impact on stress resilience

*Olivier Berton**, Sarah Teegarden, Julie Espallergues, Avin Veerakumar, Sheryl Beck

Genetic variations in several components of the glucocorticoid receptor (GR) chaperone complex have been identified as vulnerability factors for stress-related disorders. Neurobiological mechanisms that link affective resiliency to the GR chaperone complex are not well understood. Here, we provide evidence that the effects of stress hormones on affective behaviors are critically regulated via reversible acetylation of Hsp90, a key component of the GR chaperone complex. Using neuron culture, we show that selective inhibition of class 2B histone deacetylases (HDACs) leads to a hyperacetylation of Hsp90 and to blunted GR responses following hormonal stimulation. We provide further evidence in the mouse *in vivo* that this effect is mediated via the cytoplasmic lysine deacetylase HDAC6. After mapping HDAC6 cellular distribution in the mouse and human brain, we identify serotonin neurons in raphe nuclei as a critical substrate for HDAC6 influence on mouse behavior. Using a conditional

deletion approach, we demonstrate that acetylation of Hsp90, GR signaling in vivo, and behavioral sequelae of extreme stress are all regulated by HDAC6, independently of alterations in levels of histone acetylation. Selective ablation of HDAC6 from serotonin neurons is devoid of effects on the development and gross structural integrity of serotonin systems and has no impact on behavior of stress-naïve animals. However, it abrogates stress-induced translocation of the GR in raphe nuclei, and is sufficient to promote a stress-resilient phenotype in the social defeat paradigm, a murine model of PTSD, as well as in other antidepressant tests. Ablation of HDAC6 from serotonin neurons also protects serotonergic cells from the robust effects of defeat stress on their electrophysiological activity and dendritic morphology. In summary, HDAC6 constitutes a novel therapeutic target for pro-resilience and antidepressant interventions via focal antagonism of GR signaling in the serotonin system.

P29 • Exendin-4-induced glucagon-like peptide-1 (GLP-1) receptor activation reverses behavioral impairments of mild traumatic brain injury in rodents

Harold Holloway, Lital Rachmany, Vardit Rubovitch, David Tweedie, Yazhou Li, Barry Hoffer, Chaim Pick, Nigel Greig*

Mild traumatic brain injury (mTBI) represents a major and increasing public health concern and is the most frequent cause of mortality and disability in young adults. Albeit mTBI patients do not show clear structural brain defects and, in general, do not require hospitalization, they frequently suffer from long-lasting cognitive, behavioral, and emotional difficulties. No effective pharmaceutical therapy is available for mTBI, and existing treatment chiefly involves optimized intensive care management after injury. The diffuse neural cell death evident after mTBI is considered mediated by oxidative stress, glutamate-induced excitotoxicity, and is associated with neuroinflammatory processes, thereby providing potential drug targets for intervention. Our prior studies of the long-acting GLP-1 receptor agonist, exendin-4 (Ex-4), an incretin mimetic approved for treatment of type 2 diabetes, demonstrated its neurotrophic/protective activity in cellular and animal models of stroke, Alzheimer's and Parkinson's diseases, and, in line with the commonality in mechanisms underpinning these disorders, Ex-4 was assessed in a mouse mTBI model. In neuronal cultures, Ex-4 ameliorated the toxicity of both H₂O₂-induced oxidative stress and glutamate toxicity, reducing pro-apoptotic markers. To assess in vivo translocation, control and mTBI mice were administered steady-state concentrations of a clinically relevant dose of Ex-4 or saline over 7 days starting either 48 hr prior to or 1h post sham or mTBI (30 g weight drop under anesthesia). In each, Ex-4 proved well tolerated and fully ameliorated mTBI-induced deficits in novel

object recognition assessed at both 7 and 30 days post trauma. Less mTBI-induced impairment was evident in Y-maze, elevated plus maze, and passive avoidance paradigms; but here too Ex-4 induced amelioration. Together, these results suggest that Ex-4 may act as a neurotrophic/neuroprotective drug to minimize mTBI impairment, and support its clinical assessment.

P30 • The spinal central pattern generator mediates anesthetic-induced immobility across vertebrate evolution

Steven Jinks, Omar Satter, Jason Andrada, James Buchanan*

General anesthetics act in the spinal ventral horn to block organized movement. However, it is uncertain whether anesthetics target central pattern-generating (CPG) interneurons or motoneurons. We bath-separated isolated spinal cords of neonatal rats and lampreys using vaseline, restricting anesthetics to rostral or caudal spinal segments. In rats, we recorded ventral root activity during NMDA/5HT-induced fictive walking, and applied isoflurane, desflurane, or propofol to the rostral or caudal lumbar spinal cord. Thereby we distinguish anesthetic effects on the CPG from motoneurons, as others have shown CPG-mediated hindlimb rhythm generation is derived primarily from upper lumbar segments. The effects of rostral versus caudal lumbar application of all anesthetics were strikingly different. Clinical concentrations applied to the upper lumbar cord abolished fictive walking, whereas caudal lumbar application of anesthetics 3–5 times clinical concentrations did not. Rostral lumbar anesthetic application not only abolished ventral root bursting in rostral segments but also in the anesthetic-free caudal bath segments, consistent with prior studies proposing a rostral-dominant CPG. Data supporting CPG-mediated immobilizing effects were also found in the lamprey spinal cord, in which we elicited fictive swimming in the rostral segments with D-glutamate, and recorded intracellularly from motoneurons in an anesthetic-free caudal bath. Motoneurons exhibited locomotor-related membrane potential oscillations derived from the rostral bath CPG. When clinical concentrations of isoflurane or desflurane were delivered to the rostral bath, transition to immobility was associated with a near complete abolition of CPG-derived motoneuron oscillations. The data support the CPG network as the primary target for anesthetic induced immobility in both mammals and early vertebrates.

P31 • Gene X early environment interactions determine prefrontal cortex DNA methylation status and drug-seeking in adult mice

Tod Kippin, Kevin Dudley, Joannalee Campbell, K. Ploense, D. Maliniak, X. Li, W. Wei, D. K. Gascoigne, J. S. Mattick, Tim Bredy*

Addiction vulnerability is influenced by gene-environment (GXE) interactions. The present project employs a mouse model to examine the interaction between genetic background and prenatal stress (PNS) on epigenetic consequences in the medial prefrontal cortex (mPFC) and on drug-seeking behavior in adulthood. Repeated restraint stress was performed on DBA/2J (D2) and C57/BL6J (B6) mice during E14-21 of gestation, and male offspring were studied in adulthood for medial prefrontal cortex DNA methylation and cocaine-induced conditioned place preference (CPP). For DNA methylation, genome-wide DNA methylation profiling was performed using a methyl-capture microarray approach to determine PNSxStrain effects. Widely varied differences in DNA methylation (2-fold differences or greater at 1621 promoters) were observed in non-PNS D2 and B6 offspring, suggesting that underlying genetic background influences the epigenotype, which was further impacted by PNS. Interestingly, many of the genes displaying differential DNA methylation play roles in neurodevelopment and are likely responsible for the distinct behavioral phenotypes observed in later life. For CPP, mice received repeated pairings of vehicle and cocaine with distinct contexts and then tested for their preferences for each context. The impact of PNS on CPP also depended on strain with PNS increasing CPP in B6, but not D2, mice. The present data demonstrate gene-dependent impact of PNS on both mPFC DNA methylation in a highly gene-specific fashion and level of drug-seeking behavior in adult mice. Although the relation between altered mPFC epigenome and enhanced drug-seeking behavior is unclear, the present findings indicate that there are PNS-resilient (D2) and PNS-susceptible (B6) genotypes. Further, recombinant inbred strains based on genotypes of differing PNS susceptibility may be useful for examining the nature of GXE interactions and their molecular underpinnings that determine adult addiction vulnerability.

P32 • Endothelin A receptor antagonism in traumatic brain injury leads to improvement of both histopathologic and behavioral outcome

Anthony Kropinski, Justin Graves, Chris Betrus, Waqar Raza, Matt Wilson, Nate Farley, Brad Krasnick, William Armstead, Donald Kuhn, Christian Kreipke*

Decreased cerebral blood flow (CBF) is just one of the multiple pathologies observed after traumatic brain injury (TBI). Our combined laboratories have demonstrated that endothelin-1 plays a major role in the induction of

hypoperfusion. In a rodent weight drop-acceleration impact model (with male, Sprague-Dawley rats, 350–400g) of diffuse TBI, we have demonstrated that intravenous injections of endothelin receptor antagonists significantly ameliorate hypoperfusion. This current study investigates the effects of the selective endothelin receptor A (ET_A) antagonists, BQ123 and Clazosentan, a clinically relevant compound, given at various time-points on histopathologic and behavioral outcome. Neuronal injury was assessed in both TBI and TBI + treatment animals using Fluoro-Jade labeling, n = 4 per group. Behavioral outcome was determined using a radial arm maze spatial learning task, n=10 per group. Our results indicate that selective ET_A antagonism (either 1.0 mg/kg BQ-123 or 1.0mg/kg Clazosentan) causes a significant decrease both in neuronal cellular injury and improves behavioral outcome. Furthermore, by administering Clazosentan at various times points in both single and dual bolus injection paradigms we show that ET_A antagonists may be effective in ameliorating the deleterious effects of TBI if administered at specific time points post TBI. (Supported by NIH NS064976, VARR&D RX00024.)

P33 • Parkinson's disease biomarkers: Metabolomic analysis of CSF

Peter LeWitt

Preclinical markers of Parkinson's disease are needed if neuroprotective therapies are ever developed. Since dopamine metabolites are uninformative as PD biomarkers, we explored other compounds for possible disease-specific signatures. Gas chromatography–mass spectrometry and liquid chromatography–mass spectroscopy (GC-MS and LC-MS) facilitates biochemical separations and identification for investigating the human metabolome (approximately 2,000 compounds). We studied postmortem CSF collected at autopsy from clinically- and pathologically-confirmed controls (n=57; mean age: 84.3+10.5 yrs) and PD subjects (n=48; mean age: 79.9+ 6.8) with a mean postmortem interval of 3.2 hrs. CSF underwent GC-MS and LC-MS linked to an informatics platform and measuring 243 identified biochemicals and 218 unnamed compounds. Identifications were made by chromatographic properties and mass spectra. The biostatistical approach used two-sample t-tests for PD:control ratios and classification-and-regression-tree (CART) analysis with a non-parametric analytical approach to identify variables most prognostic of PD diagnosis. Using a $p < 0.02$ cutoff for identified biochemicals that had altered in PD/control ratios, 4 compounds were increased (2.66-1.25x) and 12 were decreased (0.38-0.88x). The initial CART model included several compounds with altered ratios at $p < 0.02$. N-acetyl- β -alanine, N-acetylhistidine, glucose, and

4-acetamidobutanoate remained in the final model, which had an estimated predictive ability receiver operating characteristic (ROC) of 0.88 based on learning data, and a ROC of 0.74 based on testing data using a 5-fold cross-validation approach. *Conclusions:* In postmortem CSF, we identified novel biomarkers not previously associated with PD pathophysiology. Highly-sensitive chromatographic and informatic techniques can offer insights into metabolic pathways linked to PD.

P34 • Dopamine regulation of lateral habenula neuronal activity via blockade of tonic GABA-B receptor inhibition

Carl Lupica, Cameron Good*

Activation of the lateral habenula (LHb) can strongly inhibit ventral tegmental area (VTA) dopamine (DA) neurons, signaling absence of reward. Studies have focused on the LHb to VTA connection, and not on the reciprocal VTA to LHb pathway that may also be involved in integrating the reward signal. VTA DA neuron afferents to the LHb are dense in the central subnucleus of the medial-LHb (cm-LHb). The cm-LHb also contains a dense expression of GABAB receptors. In whole-cell brain slice recordings, we found a group of cm-LHb neurons ($n = 17/31$) that were hyperpolarized at rest (-51.8 ± 1.4 vs. -40.4 ± 1.3 mV, $p < .0001$, compared to nearby neurons), and electrotonically quiescent (2.2 ± 0.9 vs. 9.2 ± 1.2 Hz, $p < .0001$). DA ($50 \mu\text{M}$) and amphetamine ($5 \mu\text{M}$) depolarized these cells, increased their firing rates, and increased the occurrence of spontaneous glutamate EPSCs (sEPSCs), suggesting the involvement of endogenous DA. Based on dense GABAB receptor expression, we evaluated whether these neurons are tonically inhibited by GABAB receptors. The GABAB antagonist CGP55845 (200 nM) mimicked the depolarizing effect of DA and the increase in sEPSC frequency. GABAB receptors couple to G-protein coupled inward rectifier k^+ channels (GIRK) that are blocked by BaCl₂. BaCl₂ (1 mM) mimicked the depolarization caused by DA and CGP55845, and occluded their effects. The BaCl₂-induced depolarization also persisted when sodium channels were blocked by TTX, indicating that tonic GABA release was impulse-independent. Our results suggest that the VTA to LHb DA projection can regulate the activity of cm-LHb neurons by reversing tonic inhibition mediated by GABA and activation of GABAB receptors. We predict that VTA DA output will act to increase cm-LHb output to downstream nuclei, and serve as a negative feedback signal to limit VTA output.

P35 • Effects on neurobehavior of lead and manganese in rats developmentally-exposed: A gender-based comparison of individual and combined exposures

Timothy Maher, Swati Betharia*

The behavioral effects of exposure to environmentally relevant low levels of the known neurotoxicants lead (Pb) and manganese (Mn) are of current interest, especially when exposure occurs during the early developmental periods of gestation and lactation. Pregnant CD rats (n=6/group) were exposed to drinking water solutions containing Pb (10 µg/ml), Mn (2 mg/ml) or a mixture, from beginning of gestation, through lactation until weaning. Monitoring of developmental parameters began on postnatal day (PND) 1. Body weight gain was measured weekly, and development of surface righting reflex was measured from PND 1 to 10. Tests of neurobehavioral were performed after weaning (PND 21-25), and repeated one month later (PND 56-60). Female pups exposed to the metal mixture were found to have significantly higher body weights through PND 56, while no such differences were seen in male pups. All metal-exposed pups exhibited faster surface righting as compared to control pups. Eye-opening in mix-exposed pups tended to occur early as compared to control pups, and was slightly delayed in Pb-exposed pups. In an open field test, Mn-exposed males were hypoactive and less impulsive than controls at PND 25. These effects remained persistent when the test was repeated on PND 60. Four-day Morris water maze tests were performed twice, ending with probe trials on PND 25 and 60. At PND 24, mix-exposed males performed significantly better, while Pb-exposed females showed deficits in learning and memory. All metal-exposed females showed impaired learning and memory on PND 57 and 60, while previous differences in male performance were no longer evident. Developmental exposures to low Pb and Mn levels can produce gender-specific subtle neurobehavioral deficits, with some effects persistent after cessation of exposures. Effects due to individual metals were found to be different from those due to the mixture, underlining the importance of studying toxicants in combination.

P36 • Mechanisms of gain-control in neural circuits revealed by nonlinear signal analysis with white noise photic stimulation

David Naylor

Unlike electrical stimulation, photic stimulation lacks stimulus artifact and can be more precisely controlled, favoring the application of nonlinear signal analysis. Sharp electrode recordings were obtained from transient amacrine cells in

catfish retina using white noise photic stimulation to generate 1st- and 2nd-order Wiener kernels. Transient amacrine cells receive inputs from both ON- and OFF- bipolar cells, and the kernels were fit using an analytic form for a parallel path L1-N-L2 “sandwich” model. The model predicts time series responses of transient amacrine cells to white noise and step inputs well (MSE < 20%). The results suggest that the strong even-order nonlinear behavior of amacrine cells suitable for contrast detection emerges from summation of even but cancellation of odd-order terms, a result of the convergence of parallel inputs of opposite polarity. The model also suggests kinetic differences between the ON- and OFF-bipolar inputs to transient cells, with the ON-bipolar impulse response being 6 msec later than that of the OFF-bipolar pathway. A greater scaling in the 2nd-order kernel relative to the 1st-order kernel (on the order of squared) occurs with increasing variance of white noise inputs, suggesting contrast gain circuitry adjustments occur before the nonlinearity (N). In conclusion, Wiener analysis and modeling of kernels reveals the highly nonlinear behavior of these cells to result from convergence of parallel inputs of opposite polarity. In addition, the mechanism for contrast gain adjustment to light levels of different modulation depth involves circuitry feedback from the inner retina to bipolar cells. The nonlinear signal analysis techniques presented are well suited to examine many neural circuits, including those modified optogenetically and directly activated by photic stimulation. In addition, the particular model construct of parallel pathways used here may be broadly applicable to many other circuits that receive opposed inputs.

P37 • Molecular determinants of NMDA receptor allosteric potentiation

Kevin Ogden, Stephen Traynelis*

NMDA receptors mediate excitatory synaptic transmission in the CNS and are candidate drug targets for a myriad of neurological diseases including traumatic brain injury, epilepsy, and schizophrenia. Several classes of compounds have been recently reported to act as inhibitors or potentiators of NMDA receptors. Moreover, these compounds appear to act at novel regulatory sites on the receptor. Here, we have investigated the functional mechanism and site of action of a class of tetrahydroisoquinolines that selectively potentiate the activity of GluN1/GluN2C and GluN1/GluN2D NMDA receptors. CIQ is a prototypical member of the tetrahydroisoquinoline class of potentiators. Removal of the amino terminal domain from either GluN1 or GluN2D did not change the actions of CIQ at these receptors, suggesting these compounds do not bind the NMDA receptor amino terminal domain. By contrast, a single-point mutation in first transmembrane helix of GluN2D (T592I) did abolish all potentiation by CIQ. We subsequently explored whether other residues in this region could

affect the actions of CIQ. Using alanine scanning mutagenesis of the GluN2D pre-M1 region and M1 transmembrane helix, we identified several residues that reduced the potency of CIQ or eliminated its activity. In a homology model of GluN1/GluN2D receptors, these residues clustered in three-dimensional space. Mutation of these critical residues in M1 did not affect other aspects of channel function, such as open probability. These data suggest that a site for positive allosteric modulation of NMDA receptors by CIQ and analogues is located in the membrane region near the gate of the receptor. Moreover, because CIQ increases NMDA receptor channel opening frequency, these data indicate M1 and the nearby pre-M1 helix could influence ion channel gating.

P38 • Evaluation of quantitative proteomics for the analysis of human plasma in search for potential neurological biomarkers

Tulen Pekny, Carina Sihlbom, Lina Bunketorp Käll, Marcela Pekna, Michael Nilsson, Milos Pekny*

Quantitative proteomics has previously been used to detect and quantify protein levels in the search for neurological biomarker molecules in biological fluids, such as blood plasma or cerebrospinal fluid. Here, we have used healthy volunteers to assess technical and interindividual variation in plasma protein levels determined by quantitative proteomics using iTRAQ labeling and nanoLC-MS/MS. This is a preparatory step for applying this approach to identify protein biomarker molecules in blood plasma of individuals in clinical studies, e.g., in a study assessing the effect of rehabilitation in long-term stroke survivors. We performed two separate protein quantifications on plasma taken from three healthy adult female volunteers (36, 38, and 58 years old) one year apart. 188 plasma proteins were quantified in a healthy individual at two time points one year apart and showed less than 20% variation between samples separately processed at the same time point. 214 plasma proteins were detected and quantified in two healthy females (36 and 58 years old) and showed less than 20% technical variation. The two experiments yielded 181 common plasma proteins which showed <20% technical variation. 127 of 181 plasma proteins showed interindividual variation of <40% and 58 of them <20%. These initial experiments suggest that the levels of many plasma proteins are stable enough to be evaluated as potential markers in neurological diseases. We plan to use unsupervised algorithms to compare plasma protein profiles between groups of stroke patients, e.g., with the aim to both predict and evaluate therapeutic success of rehabilitation therapy.

P39 • Synuclein promoter polymorphisms are associated with cognitive outcome after mild traumatic brain injury

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

Problems with attention, short-term memory, and learning, as well as speed of information processing, are commonly reported shortly after mild traumatic brain injury (mTBI). We have previously reported an association between polymorphisms in a number of genes involved in dopaminergic neurotransmission and cognitive performance following mTBI. The importance of α -synuclein (SNCA) toxicity in dopaminergic neurons and of SNCA polymorphisms as a risk factor for Parkinson's disease (PD) led us to hypothesize that SNCA polymorphisms might also be associated with cognitive outcome after mTBI. An extensively characterized, previously described cohort of 95 mTBI patients and 38 controls was genotyped at 14 single nucleotide polymorphisms in the SNCA gene. Based on our previous work, the simple reaction time condition, reaction time (SRTRT) of the Gordon Continuous Performance Test (CPT), and the California Verbal Learning Test, long delay condition (CVLT-LD) were studied as measures of speed of information processing and memory. CVLT-LD performance was associated with several tightly linked SNCA promoter polymorphisms in the mTBI patients ($p < 0.002$), but not in controls. These particular polymorphisms have not been previously linked to increased risk of PD, suggesting that the molecular biology of this association may be unrelated to the role of SNCA in the pathogenesis of PD.

P40 • Cellular engraftment into the spinal cord of NUDE rat

Monica Siegenthaler, Jason Sharp, Gabriel Nistor, Rockelle Robles, Connie Brooks, Michael McGary, Amy VanDeusen, Chris Airriess, Hans Keirstead*

The Crl:NIH-Fox1rnu rat, also known as the NUDE rat, is an athymic T-cell-deficient mouse model commonly used for tumor biology, immunology, and xenograft research. This immunocompromised rat however does have B cells and Natural Killer (NK) cells, causing concern as to whether NK cells could potentially result in rejection of grafts. NK cells are capable of distinguishing allogenic/xenogenic cells from self, triggering an effector response, and thus resulting in rejection of grafts. Therefore, there is concern regarding successful engraftment when using the NUDE rat model for studies. Here, we examine the long-term engraftment of motor neuron progenitors (MNP) derived from human embryonic stem cells (hESC) and hESCs in the spinal cord of the NUDE rat. Anti asialo GM1 antibody was administered at low and high

doses, as well as for differing durations in order to inactivate NK cells that may trigger rejection of the cells. The objective for MNP transplantation was to have successful engraftment, whereas the purpose for the hESC transplantation was to have successful engraftment accompanied by teratoma formation such that tumorigenicity studies could be performed using the engraftment paradigm. Our results demonstrate which conditions were amenable to engraftment and whether or not teratomas formed, establishing a model for future cellular engraftment and/or tumorigenicity studies into the spinal cord of NUDE rats.

P41 • A melatonin receptors heteromer regulates the daily rhythm of visual processing in mouse

Gianluca Tosini, Kenkichi Baba, Susana Contreras-Alcantara*

Previous studies have shown that melatonin modulates many retinal processes. Our previous study indicated that melatonin acting via melatonin receptors type 1 (MT1) regulates the daily rhythm in the amplitude of dark-adapted electroretinogram (ERG). In the present study, we investigate the distribution of the melatonin receptor type 2 (MT2) mRNA in the mouse retina and then the effects of its removal on the daily rhythm of the dark-adapted ERG. The results of in situ hybridization revealed MT2 transcripts were detected in the outer nuclear layer (ONL), inner nuclear layer (INL), but not in ganglion cell layer. MT2 mRNA was abundant in the ONL, the retinal layer containing the nuclei of the photoreceptor cells, and the INL, where the cell bodies of horizontal, bipolar, amacrine, and Muller cells are located. A diurnal rhythm in the dark-adapted ERG was observed in WT mice, with higher a- and b-wave amplitudes at night, this rhythm was absent in mice lacking MT2 receptors. Injection of melatonin (i.p., 1 mg/kg) during the day did not restore the amplitude of ERG and did not affect the scotopic threshold response in MT2^{-/-} mice. Injection of specific melatonin agonists MT1 and MT2 alone or in combination did not induced significant changes in the amplitude of the ERG. Administration of the melatonin antagonists Luzindole or 4P-PDOT fully blocked the effect of melatonin injections on the ERG. Our data indicate that the distribution of the MT2 receptor expression is similar to distribution of the MT1 receptor and that removal of MT2 receptor induces similar effects of those reported for the mice lacking the MT1 receptor. Our results demonstrate that the presence of both melatonin receptor types is required for the diurnal rhythm in the dark-adapted ERG, thus suggesting that MT1 and MT2 receptors may form heteromers in the photoreceptor cells.

P42 • Novel apolipoprotein-E-mimetics improve behavior, reduce neuronal loss, and reduce pathology in CV-AD and CVND-AD mice

Michael Vitek, William VanNostrand, Fengqiao Li, Dale Christensen, Carol Colton*

After age, Apolipoprotein-E4 genotype (APOE4 for gene, apoE4 for protein) is the largest risk factor for developing Alzheimer's disease (AD). In AD patients, more than half are APOE4 carriers with lower apoE-protein levels, more severe brain pathology, enhanced inflammation, and earlier memory loss. To counteract these apoE4-mediated effects, we have developed a series of apoE3-mimetic compounds known as "COG" compounds that penetrate the BBB, are neuroprotective and anti-inflammatory. To measure the effect of apoE/COG compounds, we treated CV (Tg2576-APP^{Sw}/NOS2^{-/-}) or CVND (APP^{SwDI}/NOS2^{-/-}) mice with COG compounds 3 times per week for months 10, 11, and 12. At the end of treatment, CV or CVND mice treated with subcutaneous COG compounds performed significantly better on a radial arm water maze test of learning and memory. Neuron counts showed that COG-treated animals had significantly more neurons than their vehicle-treated counterparts, consistent with the improved behavioral performance. Similarly, amyloid plaquelike and neurofibrillary tanglelike pathology were visibly reduced in COG-treated animals. Biochemical measures also showed that insoluble Amyloid Beta peptide levels were significantly reduced in COG-treated animals. Underlying these improvements, we have found that apoE/COG compounds bind and antagonize SET to reactivate Protein Phosphatase 2A, the main enzyme that removes phosphates from NFTs. The results we present will be discussed with respect to work from the literature confirming the utility of activating PP2A as a novel approach to reducing Alzheimer's disease.

P43 • Nicotine and Varenicline activate nicotinic acetylcholine receptors on GABAergic neurons in hippocampus and medial septum/diagonal band

Ursula Winzer-Serhan, Dustin W. DuBois, Joanne C. Damborsky, Annette S. Fincher, Gerald D. Frye*

Neuronal nicotinic acetylcholine receptors (nAChRs), which are involved in addiction and cognitive functions, mediate release of neurotransmitters from presynaptic sites in response to activation by an agonist. The smoking cessation drug varenicline, a partial agonist at heteromeric nAChRs, increases dopamine release but might also affect other transmitters in other brain regions. In this study, we determined nicotine and varenicline stimulated GABAergic transmission in two brain regions important for learning and memory, the hippocampus

and medial septum/diagonal band (MS/DB). Using whole-cell patch-clamp recordings in brain slices, we compared the effects of bath applications of nicotine, varenicline, and their combinations, on GABA_A receptor-mediated asynchronous, spontaneous inhibitory postsynaptic currents (mIPSCs). Indicative of increased GABA release, nicotine (10 μ M) and varenicline (10 μ M) significantly enhanced mIPSC frequency in hippocampal and MS/DB slices (K-S test, $P < 0.01$). Mean frequency was increased by nicotine in 54% and 64% of CA1 pyramidal and MS/DB neurons, respectively, and by varenicline in 78% and 46% of CA1 pyramidal and MS/DB neurons, respectively. Nicotine's enhancement of mIPSC frequency was effectively attenuated by varenicline in both brain regions, consistent with partial agonism, but when nicotine was added to varenicline exposed slices, little effect was observed consistent with varenicline's higher affinity for heteromeric $\alpha 4/\beta 2^*$ nAChRs. GABA_A mIPSC amplitude and decay kinetics were not consistently altered. These data indicate that heteromeric nAChRs are located on GABAergic presynaptic sites within the hippocampus and the MS/DB. The results are consistent with varenicline acting as a partial agonist at heteromeric nAChRs influencing GABA release onto neurons in both areas. Together, the findings potentially explaining a role for varenicline and nicotine in improving cognitive and memory function.

Tuesday, January 24, 2012

P44 • Partial monoamine loss induced by methamphetamine impairs Arc/Arg 3.1 mRNA expression in striatal efferent neurons

Melissa Barker-Haliski, Kristen Keefe*

The immediate early gene Arc (activity-regulated cytoskeleton-associated protein) is provocative because of its experience-dependent regulation, mRNA transport to and translation at activated synapses, and role in synaptic function. In this study, Arc expression induced by exposure to a novel environment was used to assess transcriptional activation and cytoplasmic expression of Arc mRNA in phenotypically identified striatal efferent neurons in the context of partial dopamine (DA) loss induced by methamphetamine (METH). This present work confirms prior observations that in normal animals more striatonigral neurons contain cytoplasmic Arc mRNA than striatopallidal neurons, despite similar numbers of these neurons showing transcriptional activation of the Arc gene. In the context of partial monoamine loss induced by METH, there is impaired cytoplasmic expression of Arc mRNA in both striatonigral and striatopallidal neurons. Breaking down the extent of DA depletion induced by METH also recapitulates earlier observations that there appears to be a

threshold level after which DA depletion cannot be compensated for in striatal efferent neurons. In this study, animals with DA depletions less than 40% show no statistically significant Arc expression differences compared to normal animals. However, in animals with DA depletion greater than 40%, there is a significant time x treatment effect on the numbers of striatal efferent neurons with cytoplasmic expression of Arc mRNA. Interestingly, recent work in a rat model of L-dopa-induced dyskinesia correlated dyskinesia severity to the expression of Arc protein levels (Sgambato-Faure, 2005), suggesting that Arc may be a novel therapeutic target for managing aberrant synaptic plasticity in the basal ganglia. Therefore, understanding the cellular processes underlying both normal and aberrant synaptic plasticity in the basal ganglia is critical to improved therapeutic treatments in the context of such partial monoamine loss.

P45 • Seizure-induced mTOR hyperactivation modulates aberrant hippocampal dendritic structure and ion channel localization in epilepsy

Amy Brewster, Angela Carter, Yan Qian, Joaquin Lugo, Anne Anderson*

Dendrites are critical regulators of synaptic integration and overall neuronal excitability. In rodent models of acquired temporal lobe epilepsy (TLE), an episode of status epilepticus (SE) results in hippocampal dendritic structural and molecular changes that leads to long-term alterations in synaptic activity and plasticity. In hippocampal dendrites, mTOR normally regulates arborization, and localization of ion channels and neurotransmitter receptors. Thus, we hypothesized that SE-induced mTOR pathway hyperactivation is a candidate mechanism underlying altered dendritic structure and ion channel dysregulation associated with SE. To evaluate this possibility, we used a rat model of acquired TLE. Rats (at postnatal day 35) were given pilocarpine to induce 1 hr of SE, or saline (Sham). Two weeks after the episode of SE or sham treatment, rapamycin (Rap) or vehicle (Veh) was administered to suppress mTOR hyperactivation (for 1 week) (n=5-8). Golgi staining revealed a dramatic disruption in the structural appearance of hippocampal CA1 dendrites in the SE + Veh group. In parallel, immunostaining showed high somatic and low dendritic staining with antibodies against Kv4.2 and HCN1 channels within CA1 in the SE + Veh group compared to Sham + Veh group. These effects in the SE + Veh group were reversed with Rap treatment. In the Rap-treated groups, golgi-stained dendrites appeared structurally more organized than in the SE + Veh group, and the Kv4.2 and HCN1 staining was shifted from the soma back to the CA1 dendrites. These findings suggest that mTOR dysregulation may contribute to the altered dendritic structure and mislocalization of ion channels following SE.

P46 • Cocaine experience dynamically alters DNA methylation at plasticity genes within the nucleus accumbens

Jeremy J. Day, David Figge, Mercy Kibe, Garrett Kaas, Daniel Childs, Kelsey Patterson, J. David Sweatt*

Exposure to drugs of abuse such as cocaine produces numerous changes in gene expression within brain reward regions such as the nucleus accumbens (NAc), which is critical for prolonged drug-induced circuit and behavioral plasticity. Epigenetic mechanisms, including methylation of cytosine bases in DNA, represent a common mechanism for enduring transcriptional control over gene expression. Recent evidence suggests that DNA methylation is a critical regulator of neuronal gene expression profiles in response to a variety of environmental experiences, including long-term behavioral memory. However, although DNA methylation machinery is known to regulate drug-induced gene expression and behavior, is currently unclear exactly how DNA methylation is altered by cocaine and how this contributes to drug-related plasticity. Here, we examined global as well as gene-specific changes in DNA methylation within the NAc following acute and repeated cocaine experience. Interestingly, repeated (but not acute) cocaine experience induced gene- and nucleotide-specific changes in DNA methylation status at a number of different plasticity gene promoters. Moreover, in some cases DNA methylation status correlated significantly with not only gene expression, but also cocaine-induced locomotor sensitization. In addition, repeated cocaine induced a global decrease in DNA hydroxymethylation in the NAc, implicating this demethylation step in cocaine plasticity for the first time. Together, these novel results suggest that DNA methylation and hydroxymethylation may contribute to the complex epigenetic regulation of transcriptional machinery in response to repeated cocaine.

P47 • Nitric oxide synthase isoform expression and activity in methamphetamine-induced striatal toxicity

Danielle Friend, Ashley Fricks-Gleason, Kristen Keefe*

Nitric oxide (NO) is heavily implicated in methamphetamine (METH)-induced neurotoxicity; however, the source of NO contributing to dopamine (DA) nerve terminal degeneration has yet to be determined. METH fails to induce DA terminal degeneration in animals with a deletion of the neuronal nitric oxide synthase (nNOS) gene and produces less damage in animals with a deletion of the inducible nitric oxide synthase (iNOS) gene. Data from our laboratory indicate that rats with a partial DA loss resulting from prior METH exposure are resistant to further decreases in striatal DA when re-exposed to

a neurotoxic regimen 7 or 30 days later. Currently, we are examining NOS expression and activity in the striata of animals pretreated with a neurotoxic regimen of METH or Saline at postnatal day (PND)60. Animals recover for 30 days and are then challenged at PND90 with either METH or Saline, resulting in four treatment groups: Saline:Saline, Saline:METH, METH:Saline, and METH:METH. The data confirm that rats with prior exposure to a neurotoxic regimen of METH are protected against further DA depletion when exposed to a second neurotoxic regimen. Analysis of nNOS and iNOS mRNA expression at 1 and 48 hr after the final treatment revealed no change in the number of nNOS-positive cells in striatum and no increase in the amount of nNOS mRNA signal per cell in animals in which METH induces DA neuron toxicity and in animals resistant to further toxicity. Also, there was no detectable iNOS mRNA in any treatment group, despite significant glial activation in rats treated with a single neurotoxic regimen of METH at PND90. These data suggest that the induction of nNOS and iNOS are not likely sources of NO implicated in METH-induced DA neurotoxicity. We are currently examining the expression of eNOS, as well as nNOS activity, to determine the role of these isoforms in METH-induced dopamine neurotoxicity.

P48 • mRNA-miRNA responses to depolarization in neuronal cells

Belinda Goldie, Murray Cairns*

Background: Prompt mRNA availability is critical in neurons, where synaptic proximity of appropriate transcripts underlies synthesis of new proteins in response to activation. As regulators of mRNA availability, microRNA (miRNA) expression may be altered by depolarization in a functionally relevant manner. *Aim:* To identify putative miRNA-mRNA regulatory networks by examining the response of these transcripts to neuronal activation. *Methods:* Depolarization conditions mimicking early- and late-phase synaptic long-term potentiation (LTP) were generated with KCl in differentiated (sequential ATRA, BDNF) SH-SY5Y human neuroblastoma. Gene and miRNA expression was analyzed by microarray and validated by qRT-PCR. Genes and miRNA with significantly altered expression were identified with GeneSpring software. Predicted targets of differentially expressed miRNA were analyzed by Functional Annotation Clustering (FAC) using DAVID online tool to investigate functional specificity; while miRNA and mRNA expression were paired in IPA software to identify putative regulatory networks. *Results:* One stimulus significantly altered expression of 105 miRNA, with a strong trend toward down-regulation (73%). After 4 serial stimuli, this was reduced to 50 miRNA with 62% downregulated. FAC revealed significant enrichment for targets involved in GPRC signalling cascades after 1 stimulus; after 4, the focus shifted to altered

transcription, RNA processing and translation. Analysis of paired miRNA-mRNA datasets found functional significance for positively correlated transcript pairs in addition to canonical negatively correlated pairings, suggesting a more complex regulatory relationship in this setting. *Conclusions:* Our data demonstrate stimulus-specific alteration of miRNA expression in neuronal cells. Targets of up- and down-regulated miRNA are significantly associated with neuronal functionality, supporting the hypothesis that miRNA act to fine-tune the response to neural activity.

P49 • Ammonia contributes to methamphetamine-induced neurotoxicity

Laura Halpin, Bryan Yamamoto*

Ammonia is a key mediator of neurotoxicity associated with peripheral organ dysfunction, including hepatic, renal, and muscular damage. In particular, ammonia has been identified as the main pathologic feature of hepatic encephalopathy, a series of neuropsychiatric symptoms following liver damage. We examined if methamphetamine (METH) produces acute hepatic damage capable of increasing brain ammonia concentrations that, in turn, contribute to the neuronal damage typically produced by METH. Male Sprague-Dawley rats were treated with METH (10 mg/kg every 2 hours x 4) and the effects on the liver were examined using H&E staining. At 2 hours after the last injection of METH, there was moderate venous and sinusoidal congestion within the liver. At 24 hours, there was considerable hepatocyte cytoplasmic disappearance. To examine if these alterations demonstrate hepatocellular damage, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured at 2 hours after the last injection of METH. METH significantly elevated serum ALT and AST by $154\% \pm 13\%$ and $231\% \pm 38\%$, respectively. Striatal ammonia levels were monitored during METH treatment using in-vivo microdialysis and showed that brain ammonia levels increased by 4-fold and persisted for at least 2 hours after the last injection of METH. In a separate group of rats, lactulose (5.3 g/kg) was administered to enhance peripheral ammonia excretion. Rats were then killed 7 days after METH treatment for the measurement of dopamine (DA) and serotonin (5HT) content. METH decreased striatal DA and 5HT content by $68.7\% \pm 6.3\%$ and $50.6\% \pm 6.9\%$, respectively, compared to saline controls. Lactulose significantly attenuated the long-term depletion of DA and blocked the 5HT depletions. In conclusion, the results show that elevated ammonia levels associated with acute hepatic damage can mediate the long-term depletions of DA and 5HT produced by METH.

P50 • PKC phosphorylates GluA1 to increase AMPA receptor conductance

Meagan Jenkins, Stephen Traynelis*

AMPA receptors are ligand-gated channels that mediate fast excitatory synaptic transmission. The C-terminal domain of AMPA receptor subunits are targeted by kinases to modulate receptor function and trafficking. Phosphorylation of GluA1-Ser818 and Thr840 by PKC alters receptor trafficking and synaptic plasticity, but it is unknown whether phosphorylation of these residues also regulates receptor function. We used variance analysis of macroscopic currents recorded from HEK cells to estimate the mean weighted conductance (γ MEAN) of recombinant AMPA receptors coexpressed with stargazin. The purified, catalytic subunit of PKC increases the γ MEAN of recombinant homomeric wild-type GluA1 receptors. To test if this resulted from phosphorylation of the GluA1 C-terminus, all known phosphorylation sites were mutated to alanine (GluA1-S818A,S831A,T840A,S845A, hereafter GluA1-AAAA). PKC did not induce a significant change in γ MEAN of these receptors. To narrow down which serine/threonine residues might be capable of mediating an increase in γ MEAN, we generated a series of phosphomimetic mutations. A glutamate substitution inserted at GluA1-Ser818, with alanine substitutions at the other three sites (GluA1-EAAA), increases GluA1 γ MEAN. The GluA1-T840E mutation (GluA1-AAEA) similarly increases γ MEAN, as does GluA1-S831E (GluA1-AEAA). These data suggest that conductance can be controlled by phosphorylation at GluA1-Ser818 Ser831 or Thr840. The increase in conductance is specific for these three residues, as phosphomimetic mutations of other residues in this region of the C-terminal domain did not affect conductance. Synaptic plasticity studies have focused on GluA1-Ser831 phosphorylation by CaMKII, but PKC phosphorylation of GluA1 at additional residues may have an equally important role. Understanding the mechanisms that underpin phospho-dependent regulation of GluA1 can yield insight into the molecular changes that occur during activity-dependent synaptic plasticity.

P51 • The development of lead compounds for the next generation of antidepressants?

Claus Løland, Mads Larsen, Per Plenge, Klaus Bøgesø, Jacob Andersen, Anders Kristensen*

The serotonin transporter (SERT) controls synaptic serotonin levels and is the primary target for antidepressants (ADs) including selective serotonin reuptake inhibitors, e.g., S-citalopram (S-CIT), and tricyclic antidepressants, e.g., clomipramine. In addition to a high-affinity binding site, SERT possesses a low-affinity allosteric site for ADs as assessed by their ability to inhibit dissociation of high-affinity bound radioligand ([³H]S-CIT). We have recently localized

the allosteric site to the extracellular vestibule above the substrate binding site (S1) corresponding to the S2 site in the SERT homologue LeuT. The faster onset of action of S-CIT compared to the racemic drug has been shown to be due to its allosteric properties, thus, the binding of ligands with specificity towards the S2 site have potential clinical implications. Here, we wanted to identify ligands with high selectivity for the S2 site that could be used as lead compounds for the generation of high-affinity, high specificity S2 binders. The citalopram analogue, talopram, has low affinity for the SERT; and thus we tested all substituents between citalopram and talopram for their binding properties to the S1 and S2 site. The S1:S2 site selectivity ratio of S-CIT 1000-fold, whereas talopram had no significant binding to either of the sites. Interestingly, of all the tested analogues, two had allosteric potency better than S-CIT (~2-fold). In addition, they possessed very poor affinity to the S1 site and, thus, were more selective towards the S2 site than any previously studied compounds. Also, the data showed that the cyano-group of the substituents were crucial for obtaining S2 potencies and the dimethyl group on the furan ring from talopram improved the allosteric potency as well as caused a profound decrease in its S1 affinity. Further substitution, as well as the introduction of mutations in the S2 site, will provide more information about the determinants of high-affinity S2 binders in SERT.

P52 • Opioid-sensitive GABA inputs from rostromedial tegmental nucleus synapse onto midbrain dopamine neurons

Aya Matsui, John Williams*

Opioids increase dopamine release in the brain through inhibition of GABA-A IPSCs onto dopamine cells. Immuno-labeling indicates that GABA neurons in the rostromedial tegmental nucleus (RMTg), also known as the tail of the ventral tegmental area (tVTA), send a dense projection to midbrain dopamine neurons stain for μ -opioid receptors. There is, however, little functional evidence that these neurons play a role in the opioid-dependent increase in dopamine neuron activity. The present study used retrograde tracers injected into the ventral tegmental area (VTA) to identify RMTg neurons that project to the VTA. Whole-cell current clamp and cell-attached recordings from labeled RMTg neurons were carried out in sagittal slices from rat. The rhythmic spontaneous firing rate of RMTg neurons was decreased and the membrane potential was hyperpolarized in response to application of μ -opioid agonist DAMGO. However, kappa and delta opioid agonists (u69593 and DPDPE) failed to hyperpolarize in RMTg neurons. Whole-cell recordings made in dopamine neurons revealed rhythmic, large-amplitude spontaneous IPSCs that had a similar frequency, pattern, and opioid sensitivity to the firing of RMTg neurons. In addition, electrical and channelrhodopsin2 stimulation within the

RMTg evoked GABA-A IPSCs in dopamine neurons that were inhibited by μ -opioid agonists DAMGO, but not kappa and delta opioid agonists. Channelrhodopsin2 were also used to evoke GABA-A IPSC from another GABA inputs to dopamine neurons, such as striatum and VTA interneurons. The opioid sensitivity to each pathway was examined to answer the relative role in RMTg to opioid actions. This study demonstrates functional connection from the RMTg to the VTA mediated by a dense, opioid sensitive GABA innervation, and that the RMTg is a key structure in the μ -opioid receptor dependent regulation of dopamine neurons.

P53 • TRPC1 and TRPC3 channels regulate intracellular calcium homeostasis and visual sensitivity in the mouse retina

Tunde Molnar, Peter Barabas, Wei Xing, Claudio Punzo, David Krizaj*

Canonical type transient receptor potential channels (TRPCs), first identified by homology with *Drosophila* TRP channels, are Ca^{2+} -permeable nonselective plasma membrane cation channels that are widely expressed in neuronal tissues. TRPCs can be activated by stimulation of G protein-coupled receptors through the PLC/DAG pathway but may also contribute to store-operated Ca^{2+} entry (SOCE). The purpose of this study was to characterize SOCE in mouse rods, to identify its molecular mechanism, and to determine the functional roles for specific TRPC isoforms in mouse visual behavior. Resting, depolarization- and SOCE-mediated $[\text{Ca}^{2+}]_i$ was determined using calcium-imaging in fura-2 loaded rods. Depletion of internal stores with cyclopiazonic acid (CPA) in Ca^{2+} -free medium evoked sustained $[\text{Ca}^{2+}]_i$ overshoots following the return to Ca^{2+} -containing medium - a response typical of SOCE. Resting and SOCE-mediated $[\text{Ca}^{2+}]_i$ levels were unaffected by blockers of voltage-operated and cyclic nucleotide-gated ion channels (CNG) but were suppressed by La^{3+} and SKF96365. Using RT-PCR, we found all 7 *Trpc* genes present in the mouse retina. The two most prominent expressed mRNAs encoding *Trpc1* and *Trpc3* were both localized to photoreceptors. Ablation of *Trpc1* and *Trpc3* genes had no effect on resting and SOCE $[\text{Ca}^{2+}]_i$ levels in KO rods. We also investigated rod-dominated (scotopic) and cone-dominated (photopic) synaptic transmission and visual behavior in *Trpc1* and *Trpc3* knockout mice. TRPC1 and TRPC3 KOs showed supralinear ERG responses to light flashes together with enhanced behavioral sensitivity compared to wild type mice. In summary, our data shows that SOCE represents a significant Ca^{2+} influx component in mouse rod photoreceptors and that TRPC1 acts in synergy with TRPC3 to regulate rod-mediated signaling in the mouse retina. These results point at intriguing new parallels between invertebrate vision dominated by TRP channels and signaling pathways in mammalian rods.

P54 • Serial exposure to stress and methamphetamine results in persistent alterations in the structure and function of the blood brain barrier: Role of neuroinflammation

Nicole Northrop, Bryan Yamamoto*

Methamphetamine (Meth) is a widely abused psychostimulant. Since drug abuse and stress are highly comorbid, it is important to study the toxic effects of Meth in the context of stress. Furthermore, prior exposure to stress enhances Meth-induced monoaminergic damage. The mechanisms by which this damage occurs appear similar to the mechanisms that cause damage to the BBB. In fact, high, seizure-producing doses of Meth transiently increase blood brain barrier (BBB) permeability, but nothing is known about the effects of the combination of stress and Meth on the BBB. We hypothesized that serial exposure to mild chronic unpredictable stress (CUS) and a moderate dose of Meth would alter the structural components and function of the BBB. To test this hypothesis, male Sprague-Dawley rats were exposed to 10 days of CUS or handling. Subsequently, rats were treated with Meth (7.5 mg/kg x 4 ip, q 2hr) or saline on the day after the last stressor. After 24 hrs, there were no changes observed in response to Meth alone. In contrast, the combination of Meth and CUS produced a decrease in expression of the tight junction proteins, occludin and claudin-5, and an increase in truncation of β -dystroglycan, brain water, and FITC-dextran extravasation. With the exception of the increased FITC-dextran extravasation, these effects were prevented by the anti-inflammatory, ketoprofen, administered during Meth. All changes other than β -dystroglycan and brain edema persisted for 7 days, were paralleled by increases in GFAP, and were blocked by ketoprofen administered during and after Meth treatment. These results indicate that CUS and Meth synergize to produce long-lasting structural and functional BBB disruptions through pro-inflammatory mechanisms. In addition, this is the first evidence that combined but not singular exposure to stress and Meth may produce a long-lasting vulnerability of the brain to subsequent environmental insults resulting from the persistent breach of the BBB.

P55 • Subunit-selective allosteric inhibition of glycine binding to NMDA receptors

Kevin Ogden, Kasper Hansen, Stephen Traynelis*

NMDA receptors are ligand-gated ion channels that mediate fast excitatory neurotransmission in the brain, and are involved in numerous neuropathological conditions. The differential expression of NMDA receptor subtypes in the CNS offers promise that a subunit-selective antagonist would modulate aberrant receptor function in a region- and circuit-specific manner. To facilitate the development of novel therapeutic agents, it is important to identify

modulatory binding sites on the NMDA receptor. Upon simultaneous binding of co-agonists glycine and glutamate to the GluN1 and GluN2 subunits, respectively, NMDA receptors undergo conformational transitions that culminate in opening of their ion channel pore. Ligands binding to modulatory sites distinct from the agonist binding sites potentially allow pharmacological intervention with mechanisms that could be well-tolerated and therapeutically beneficial. TCN-201 is a GluN1/GluN2A-selective antagonist whose inhibition can be surmounted by glycine. We investigated the mechanism by which TCN-201 inhibition can discriminate between GluN2 subunits and, at the same time, be surmounted by binding of agonist to the GluN1 subunit. We observe that binding of TCN-201 reduces potency of agonists at the GluN1 subunit and vice versa, but does not reduce potency of the GluN2 agonist glutamate. We show that binding of TCN-201 is accelerated in the presence of glutamate alone, but slowed in the presence of glycine alone. Furthermore, TCN-201 binding accelerates glycine deactivation. We identify a residue located at the dimer interface between the GluN1 and GluN2 agonist binding domains that controls the subunit-selectivity of TCN-201 inhibition. Our results suggest TCN-201 binds to a novel allosteric site located at the dimer interface between the GluN1 and GluN2 agonist binding domains, and demonstrate that TCN-201 is a negative allosteric modulator of glycine binding.

P56 • Mg²⁺-dependent modulation of cell-cell coupling and voltage gating in neuronal gap junction channels

Nicolas Palacios-Prado, Michael V. L. Bennett, Feliksas F. Bukauskas*

Changes in the cytosolic concentration of Mg²⁺ ions may occur during physiological and pathological conditions, such as hypoxia and ischemia, causing significant changes of electrical and metabolic cell–cell communication through gap junction (GJ) channels. To study the mechanisms by which Mg²⁺ modulate channel gating, we examined junctional conductance (gj) and gj dependence on transjunctional voltage (V_j) in HeLa cells expressing Connexin36 (Cx36), Cx45 and Cx47, all of which are expressed in neurons of the CNS. To control [Mg²⁺]_i, we used pipette solutions containing different concentrations of MgCl₂, MgATP, K₂ATP, or EDTA. We fitted the gj–V_j relations using a stochastic four-state model containing a V_j-sensitive gate in each apposed hemichannel (aHC) to estimate gating parameters characterizing sensitivity to voltage and the number of functional channels (NF) that can be gated by V_j. Homotypic Cx36 GJs, which is the most largely expressed neuronal GJs, exhibited a marked effect in gj when free [Mg²⁺]_i was modified in both pipette solutions. In experiments using different [Mg²⁺]_i pipette and relatively constant [Ca²⁺]_i pipette (5 mM EGTA; 2 mM BAPTA) we observed ~3.5-fold increase in gj at [Mg²⁺]_i pipette=0.01 mM, and almost complete uncoupling at

[Mg²⁺]_i pipette = 5 mM with pK = 0.4 mM. High free [Mg²⁺]_i caused increased sensitivity to voltage, while low free [Mg²⁺]_i caused the opposite effect. Homotypic Cx45 and Cx47 GJs exhibited reduction in g_j under high free [Mg²⁺]_i by increasing sensitivity to voltage and decreasing open channel probability. Single-channel conductance of Cx45 and Cx47 did not change under low or high free [Mg²⁺]_i. Asymmetric [Mg²⁺]_i pipette conditions resulted in asymmetric g_j-V_j dependence, suggesting a direct interaction of Mg²⁺ ions with the channel pore. In summary, Mg²⁺ significantly modulates g_j by changing sensitivity to voltage of aHCs and NF of neuronal Cxs expressed in CNS.

P57. Simultaneous representation of goal information and hand kinematics in dorsal premotor cortex during reach planning and execution

Thomas Pearce, Daniel Moran*

Humans and nonhuman primates are adept at making reaching movements to visually identified targets. These actions are not limited to simply translating the hand directly from a starting position toward the goal; the control system must be able to account for any constraints on potential movement trajectories and guide the hand appropriately. The neural substrate that supports this ability to turn visual information into an appropriate set of muscle activations is thought to include the dorsal premotor cortex (PMd), located just rostral to the primary motor cortex. This study presents evidence that during the planning of reaching movements that take an indirect path toward the target in order to avoid obstacles in the environment, both the initial movement and target directions are simultaneously represented in the firing rates of PMd neurons. Subpopulations of neurons preferentially encode either the target or movement directions, while many neurons carry information about both target and hand direction. The population-level representations of these variables evolve on a similar time course and are maintained through an instructed delay, indicating that movement direction as well as goal information is planned as soon as relevant trajectory information is available to the animal. Replicating prior studies, population activity can be used to decode instantaneous hand velocity during movement. In addition, a stable representation of the target direction relative to the starting hand position is maintained throughout the movement, regardless of the instantaneous hand position or velocity. These data shed new light on the neural circuitry involved in planning and executing complex reaching movements.

P58 • D1 dopamine receptors in the nucleus accumbens are critical for enhanced amphetamine reward and nucleus accumbens deltafosb accumulation caused by sexual experience in male rats

Kyle Pitchers, Lique Coolen*

Sexual experience in male rats causes facilitation of mating behavior, sensitization of amphetamine reward, morphological and transcriptional changes in the nucleus accumbens (NAc). Here, we determine whether D1 or D2 dopamine receptors (D1R, D2R) in the NAc mediate the effects of sexual experience on enhanced amphetamine reward and the accumulation of deltaFosB. Sexually naïve adult male Sprague Dawley rats were implanted with bilateral cannulas directed at the NAc. During each of 4 daily mating sessions, males received infusions of either D1R antagonist SCH23390, D2R antagonist eticlopride, or saline (Sal). Then, males mated to one ejaculation (sexually experienced; Exp) or were placed in the test cage without a female (sexually naïve), creating 4 experimental groups: Naïve-Sal, Exp-Sal, Exp-D1R, and Exp-D2R. One week after last mating session or handling, AMPH reward was measured using a conditioned place preference (CPP) paradigm consisting of a single pairing with 0.5 mg/kg AMPH (s.c.). Similar to previous findings, Exp-Sal males formed a CPP for this low dose of AMPH, while Naïve-Sal animals did not. Moreover, D1 receptor activation in the NAc during sexual behavior is critical for the sexual experience-induced sensitized AMPH reward as Exp-D1 males did not form a CPP, whereas Exp-D2R animals did form CPP. Next, all animals were perfused for quantification of NAc deltaFosB levels using immunohistochemistry. Sexually experience-induced deltaFosB in NAc in Exp-Sal and Exp-D2R groups were significantly greater compared to sexually naïve controls. D1R antagonism blocked NAc deltaFosB accumulation as expression in Exp-D1 groups was significantly lower than both other sexually experienced groups (Sal and D2R). Together, these findings demonstrate that activation of the D1R in the NAc is critical for the effects of sexual experience on sensitized AMPH reward and the accumulation of deltaFosB in the NAc.

P59 • The mechanosensitive cation channel TRPV4 is a major regulator of calcium homeostasis in radial astroglia of the vertebrate retina

Daniel Ryskamp, Shiwani Chauhan, Amber Frye, Tünde Molnár, Péter Barabás, Wei Xing, David Križaj*

Müller cells are radial astroglia that regulate ionic flux, pH, neurotransmitter recycling, and neurotrophic factor secretion in the retina. Mechanical trauma, retinal detachment, diabetes, and glaucoma detrimentally impact Müller cell-mediated homeostatic functions critical to the survival of retinal cells. In response to these pathological conditions and others, reactive Müller glia can also exacerbate retinal injury through hypertrophy and/or proliferation. Calcium signals substantially contribute to the response of Müller cells to retinal distress; however, the mechanisms through which these cells sense mechanical trauma have remained enigmatic. Here, we show that calcium homeostasis in mouse Müller glia is prominently regulated by the mechanosensitive cation channel transient receptor potential vanilloid 4 (TRPV4). The amplitudes of intracellular calcium signals evoked by TRPV4 agonists far exceed that of known modulators of glial calcium levels (e.g., ATP, glutamate, high $[K^+]_o$). The TRPV4 agonist GSK1016790A (GSK) evoked calcium elevations that exceeded $1 \mu M$ and persisted for 10s of minutes, in sharp contrast to transient, desensitizing responses observed in retinal ganglion neurons. Müller glia responses to GSK were completely blocked by the selective TRPV4 antagonist HC 067047. Consistent with calcium entry mediated by a plasma membrane ion channel, GSK responses were dependent on external calcium, whereas release from internal stores constituted a small fraction of the overall TRPV4 response. Mechanical stimulation of Müller glia evoked sustained cytosolic calcium elevations. The TRPV4 antagonist HC 067047 significantly reduced the percentage of Müller glia responding to membrane stretch. In summary, we have identified a novel mechanism through which retinal astroglial cells sense and transduce mechanical stimuli. This suggests the TRPV4 channel as a plausible target in debilitating blinding diseases such as ischemia, diabetic retinopathy and glaucoma.

P60 • Abnormalities of FKBP5 and BAG1 within the glucocorticoid receptor stress signalling pathway in schizophrenia and bipolar disorder

Duncan Sinclair, Stu Fillman, Nicole Cloonan, Cyndi Shannon Weickert*

Abnormal patterns of stress hormone secretion, under basal conditions and in response to stress, are found in individuals with schizophrenia and bipolar

disorder. These psychotic illnesses are associated with altered glucocorticoid receptor (GR) expression in the brain. However, it is not known whether other components of the cellular GR-mediated stress signalling pathway may also be dysregulated in psychosis. Such components could include chaperones and stress receptor cofactors, which are important for the folding and trafficking of GR, as well as for facilitating and repressing GR-mediated transcriptional activation of target genes. In this study, we used quantitative real-time PCR to explore the mRNA expression of six GR chaperones and cofactors—HSPA1A, HSP90AA1, DNAJB1, HSP27, BAG1, and FKBP5—in the dorsolateral prefrontal cortex of 35 schizophrenia, 35 bipolar disorder, and 35 control cases. No diagnostic differences in HSP mRNA expression (HSPA1A, HSP90AA1, DNAJB1, HSP27) were observed. However, opposing changes in FKBP5 and BAG1 mRNA expression were identified. FKBP5 mRNA expression was significantly increased in schizophrenia cases (68.0%, $p < 0.001$) and bipolar disorder cases (47.5%, $p < 0.05$) relative to controls. In contrast, BAG1 mRNA expression was significantly decreased in both schizophrenia (12.1%, $p < 0.05$) and bipolar disorder (14.9%, $p < 0.005$) relative to controls. GR mRNA levels were significantly negatively correlated with mRNA levels of FKBP5 and all HSPs but positively correlated with BAG1 mRNA levels. Next generation sequencing of an additional, independent schizophrenia cohort (20/20) also revealed increased FKBP5 mRNA expression in schizophrenia, and highlighted additional changes in genes associated with stress signalling networks. These findings reveal possible dysregulation of FKBP5 and BAG1 expression in schizophrenia and bipolar disorder, and suggest that a network of interrelated changes may impact stress signalling in psychotic illness.

P61 • Latent inhibition is impaired by brain adenosine hypofunction: An adenosinergic link to schizophrenia-related attentional dysfunction

Philipp Singer, Detlev Boison, Ben Yee*

Adenosine is a ubiquitous neuromodulator, and its deficiency in the brain has been linked to schizophrenia symptom genesis. This may be mediated by adenosinergic modulation of cortical neural plasticity and/or adenosinergic control over subcortical arousal. To distinguish between them, two transgenic mouse lines carrying opposite changes in extracellular adenosine in the cerebral cortex were generated by conditional deletion of adenosine kinase (ADK)—the key enzyme of adenosine clearance: Adk-tg mice were characterized by ADK overexpression in the entire brain and therefore global adenosine deficiency, whilst fb-Adk-tg mice carried a telencephalon-specific ADK disruption introduced into the Adk-tg background. A form of learned inattention—latent inhibition

(LI)—impaired in schizophrenia patients was examined in these mutant mice in a conditioned taste aversion paradigm. LI is demonstrated as a retardation of conditioned aversion to a distinct taste that has been paired with sickness due to prior preexposure of the to-be-conditioned taste stimulus. Compared with wild-type controls, LI was completely abolished in Adk-tg mice. In contrast, the impairment seen in the fb-Adk-def mice was incomplete. Together, our data are supportive of (1) the adenosine hypofunction hypothesis of schizophrenia, and (2) the antipsychotic potential of cortical ADK inhibition. The present study clearly shows that LI is jointly but differentially regulated by cortical and sub-cortical adenosinergic mechanisms. Adenosine, as well as ADK, thus represents a versatile drug target for the fine-tuning of a form of selective attention central to both positive and negative schizophrenia symptoms.

P62 • Physiological normoxia enables reliable and efficient generation of neural precursor cells, motor neurons, and dopaminergic neurons from human embryonic stem cells

Sybil Stacpoole, Bilada Bilican, Daniel Webber, Aryna Luzhynskaya, Alastair Compston, Ragnhildur Karadottir, Robin Franklin, Siddharthan Chandran*

Standard cell culture conditions employ oxygen tensions approximating that of room air. This is far removed from the physiological situation, especially in the context of the stem cell niche and the nervous system, where oxygen levels may vary from 0.55% to 8%. We investigate whether an ambient environment containing a physiological oxygen level of 3% can allow the generation of neural precursor cells (NPCs) from human embryonic stem cells (hESCs) and whether this system provides advantages over the hyperoxic 20% conditions. We find that there is a clear survival benefit when generating NPCs from hESCs in a normoxic environment, which can be partly reproduced by the use of anti-oxidants at 20% oxygen. We report a transient upregulation of HIF-1 α protein, and postulate that this reflects adaptation to the lower oxygen environment, with HIF-2 α maintaining a physiological response. This system uses feeder-free ES cells and a chemically defined, serum-free medium; the resulting normoxic (3% O₂) NPCs demonstrate tri-lineage potential and electrophysiological maturation of neurons. These normoxic NPCs can be successfully directed to differentiate into dopaminergic and motor neurons, with 2- to 5-fold higher efficiency than at 20% oxygen. Differentiated neurons can be maintained in culture for months, without the requirement for exogenous neurotrophic support, providing a platform through which basic biological questions can be posed. Finally, transplantation of normoxic NPCs into the neonatal rat hippocampus

gave an indication of an initial survival advantage. Overall, the system described here affords a novel approach to both the generation of defined cell types for in vitro studies and for transplantation therapies, and the approach to transplantation itself.

P63 • Prior trauma moderates amygdalar connectivity during “unseen” cues in cocaine-dependent patients

Jesse Suh, Ronald Ehrman, Teresa Franklin, Kanchana Jagannathan, Ze Wang, Yin Li, Zachary D. Singer, Marina Goldman, Charles P. O’Brien, Anna Rose Childress*

Prefrontal cortex (PFC)–amygdala (AMYG) circuitry is responsible for top-down modulation of emotional arousal. We previously reported that cocaine dependent (CD) patients with a prior trauma history showed an increased limbic brain response to cocaine and aversive cues, suggesting that trauma-exposed CD patients have a “cue-sensitive” brain. We hypothesized that CD patients with trauma would have compromised circuitry between AMYG and PFC and the anterior cingulate (ACG). We used event-related BOLD fMRI to measure the brain response to neutral, cocaine, aversive and sexual cues of 33msec duration with 467msec neutral stimulus backward-mask to prevent conscious recognition. Data were preprocessed within SPM2. We used the task-related partial least square (PLS) analysis, and seed voxel PLS was then used to contrast the functional connectivity between groups and across conditions based on trauma history (9 Trauma vs. 10 No-Trauma). The significant latent variable (LV) ($p < 0.001$) differentiated the two groups during cocaine, aversive and sexual cues. No-trauma group showed a task-related activity in ACG and AMYG. Based on the role of AMYG in arousal/emotion, we used left AMYG as a seed region within the functional connectivity to identify the emotive networks that are active during “unseen” stimuli. The dominant LV for seed voxel PLS ($p < 0.0001$) revealed a main effect of tasks, showing stronger positive AMYG connectivity in insula and ACG during cocaine stimuli. In second LV ($p < 0.0001$), trauma maintained stronger positive AMYG connectivity in insula, OFC and DMPFC and no-trauma showed stronger negative AMYG connectivity in dorsal ACG during cocaine and aversive stimuli. Overall, prior trauma is associated with stronger intra-limbic connectivity, whereas no-trauma group demonstrated top-down modulation. The PFC-AMYG circuitry may serve as a potential marker of a general modulatory failure that may underlie vulnerability to stress-related relapse in CD.

P64 • Elevated low-frequency power across resting, sensory, and cognitive conditions in schizophrenia

Elyse Sullivan, Ann Summerfelt, Patricio O'Donnell, Elliot Hong*

Cognitive deficits such as those involving working memory and sustained attention are common features in patients with schizophrenia (SZ). Electrical oscillatory abnormalities have been found in SZ patients compared to normal controls in diverse conditions such as perceptual processing, sensory processing, and working memory tasks. We designed auditory tasks to look at sensory perception as well as working memory and sustained attention. We aimed to examine if there are any oscillatory differences in patients that may be present regardless of condition and/or reflect cognitive impairments. Using a discrete wavelet decomposition technique, we extracted single-trial time-frequency components of auditory evoked potentials. In the continuous matching task (CMT), which requires sustained attention and working memory, there was no difference in the performance between SZ and controls. However, there was a significant elevation of low-frequency power, i.e., delta at 1–4Hz, and theta-alpha at 5–12Hz in patients compared to controls that was most evident in the midline channel Fz. A similar low-frequency (1–4 Hz delta) power elevation in SZ patients was observed during a simple passive sensory condition and during a non-stimulated resting condition. This indicates that although sustained attention did not appear to be compromised in SZ patients performing this task, there were differences in EEG oscillatory activity compared to controls. The low-frequency power elevation may represent a sort of context-invariant endophenotype associated with SZ. Additionally, in the CMT task, we found that both patients and controls showed a significant decrease in gamma power (21–85 Hz) during error trials compared to correct trials. Thus, decrease in gamma power may be associated with transient cognitive difficulties or errors during performance.

Wednesday, January 25, 2012

P65 • Dietary melatonin reverses age-related elevations in inflammatory genes and also reduces tumor size and number in aged mice

Stephen Bondy, Kaizhi Sharman, Edward Sharman*

A series of studies were originally designed to explore the potential of melatonin for reducing the rate of onset of some genetic indices of brain aging. Using many sets of male mice in several experiments performed during a nine-year period, it was found that basal levels of expression of many pro-inflammatory genes are

elevated with age even in the absence of an exogenous provocative stimulus. This elevation was largely reversed by treatment with dietary melatonin. When animals were sacrificed, they were routinely examined for evidence of tumors; and when these were found, a note was made of their occurrence and of their size. In addition to restoring a more youthful gene expression profile, melatonin-supplemented mice aged ≥ 26 months at sacrifice had significantly fewer tumors with lower severity than similarly aged control animals. As judged by overall mortality rates, longevity was also increased by melatonin. Since tumorigenesis was not the original intent of the study, these observations were recorded but not pursued in greater detail. In this report, these data have now been collated and summarized. This analysis has the disadvantage that tumor origin and morphology were not recorded. However, the study also has the advantage of being conducted over an extended period of time with many groups of animals. In consequence, many extraneous factors, which could be potential confounders, such as seasonal or dietary variations, are unlikely to have interfered with the analysis. Furthermore, the strains of mouse used were selected for longevity and were not cancer-prone until aged. The tumor incidence in animals younger than 25 months was very low. The use of more than one mouse strain strengthens the possibility that the findings may have general relevance.

P66 • Deciphering the role of myostatin in sarcopenia and neuromuscular degeneration in aging

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

Lower body composition seems to influence the rate of cognitive decline in subjects with mild cognitive impairment (Cronk, 2010), and poor handgrip strength can also predict cognitive decline in the oldest old (Taekema, 2010). These results, among others, highlight the need to find therapies that increase not just muscle mass but also strength in sarcopenic individuals. About 15 million older Americans are sarcopenic, and accompanied by physical disability, to an estimated financial burden of \$18.5 billion per year. There is much interest in developing anti-myostatin (Mst) agents to counteract muscle atrophy. So far, only one safety trial of an anti-Mst antibody has been conducted in human subjects with muscular dystrophy (Wagner, 2008). Although the acquisition of muscular strength requires neural involvement, no studies have addressed whether or how Mst inhibition affects the innervation of skeletal muscle. We have started to examine the interaction between Mst and the nervous system at the molecular and behavioral levels, using a unique animal model, the CMOT mouse (Conditional Myostatin Overexpression Transgenic) in which expression of this protein is under experimental control, using a genetic on/off switch

driven by doxycycline administration in the diet. We describe that high levels of Mst induce a significant ($p=0.0015$) increase (31%) in spontaneous activity (increase in the number of visits to the drinking corners, without changes in the number of licks to the water bottle). This is accompanied by generalized atrophy, and an increase in the percent of slow fibers in several muscles of the hind limb. The increase in Mst protein also correlates with an increase in the expression of ActRIIB receptor in brain, suggesting a possible mechanism for the interaction between Mst and the nervous system.

P67 • Vector-mediated delivery of clostridial C3 transferase to enhance spinal regeneration

David Fink, Marina Mata*

Regeneration of the central sensory and motor axons is blocked by the growth inhibitory effects of chondroitin sulfate proteoglycans (CSPG) in the glial scar and myelin proteins NogoA, myelin associated glycoprotein (MAG) and oligodendrocyte myelin glycoprotein (OMgP). Myelin protein inhibitors and CSPGs exert their growth inhibitory effects through activation of Rho dependent signaling to regulate actin cytoskeleton and microtubule polymerization. Clostridial C3 transferase (C3t) is a bacterial protein that inhibits Rho signaling by N-ADP ribosylation of Rho GTPases. In order to selectively express C3t in injured neurons and their growing axons, we constructed a non-replicating herpes simplex virus (HSV)-based vector carrying two copies of the bacterial C3t gene (vC3t). We report the regenerative response of ascending CNS axons following delivery of vC3T by subcutaneous inoculation to express C3t selectively in DRG neurons in cervical root injury, and of descending tracts by direct inoculation of cortical motor neurons after cervical hemisection injury.

P68 • Naturally occurring neuronal apoptosis and caspase-3 activation in the brains of adult control rats and those with prolonged seizures

Denson Fujikawa

Naturally occurring apoptotic neurons that are mostly active caspase-3-negative are present in the brains of untreated adult rats. In this study, we determined if prolonged epileptic seizures affect either the numbers of, or caspase-3 activation in, these naturally occurring apoptotic neurons. Adult male rats underwent either 3-h lithium-pilocarpine-induced status epilepticus (SE) and a 6 h or 24 h recovery period or lithium chloride and saline injection and equivalent periods of observation in controls. Following transcardiac in situ brain perfusion-fixation, their brains were removed and their left hemispheres were processed for paraffin embedding, coronal sectioning, and staining with TUNEL and an

antibody to the active p17 fragment of caspase-3 (CM1 antibody). The total numbers of TUNEL-positive apoptotic neurons and the numbers in 7 of 24 brain regions were increased 6 h but not 24 h following SE. At both 6 and 24 h, the total number of CM1 antibody-positive apoptotic neurons were substantially fewer in both control and SE groups (2% and 17% at 6 h and 1% and 2% at 24 h, respectively), and the numbers of CM1 antibody-positive apoptotic neurons did not differ significantly between groups. SE can affect the numbers of naturally occurring apoptotic neurons in the adult rat brain, but the numbers of active caspase-3-immunoreactive apoptotic neurons are not affected by SE. The relatively few naturally occurring apoptotic neurons must be recognized, so that they are not confused with the numerous and widespread seizure-induced caspase-3-independent necrotic neurons that show the DNA fragmentation characteristic of programmed cell death.

P69 • Effects of self-vocalization on human subcortical firing

Jeremy Greenlee, Richard Reale, Haiming Chen*

The use of deep brain stimulation (DBS) has become an effective treatment for movement disorders including Parkinson's disease, Essential Tremor, Dystonia. In addition, DBS is being investigated for other diseases such as depression, obsessive-compulsive disorder, epilepsy, and obesity. With regards to Parkinson's disease, DBS has been demonstrated to be superior to best medical management and improve patient's quality of life. Despite the efficacy of DBS in improving the motor function of the extremities, it is becoming more apparent that the motor speech of patients treated with DBS often deteriorates. The mechanisms of this paradoxical observation involving motor systems remain unclear. In addition, differential effects of DBS on motor speech depending on whether the globus pallidus interna (GPI) or subthalamic nucleus (STN) is the target of DBS are not clear. In order to gain insight into the motor speech control of Parkinson's patients, we are recording subcortical neuronal activity of these patients during DBS implantation surgery with invasive microelectrode recording (MER). MER is taken while patients perform sustained vowel vocalization (/a/), with and without pitch-shifted real-time auditory feedback. Speech stimuli and simultaneous MER is obtained from dorsal, middle, and ventral portions of the subcortical nucleus targeted during surgery (STN or GPI). Left and right target nuclei are examined in each subject undergoing bilateral surgery. Preliminary findings show that both STN and GPI firing rates increase during self-vocalization, but only within subregions of each nucleus. In addition, some portions of the nucleus show increased firing beginning at the onset of pitch-shifted auditory feedback. Increased firing rates have been observed in both the left and right nuclei.

P70 • Neurofeedback: Panacea? Placebo? Parachute?

Eric Harris, Lauren Frey*

Neurofeedback (NF) refers to operant conditioning in which a subject performs no physical tasks and reward is contingent upon modifying specific features of spontaneous EEG or EEG evoked responses. The therapeutic potential of NF was discovered serendipitously 40 years ago in an investigation in cats of the epileptogenic properties of rocket fuel. Subsequently, NF was successfully applied to the treatment of refractory epilepsy, and since has been investigated and shown promise for treating a variety disorders including ADHD, migraine, and autism. Because NF is noninvasive, comparatively safe, and can yield long-lasting benefits for a variety of conditions, it seems like a panacea. On the other hand, despite NF being widely used, the growing body of evidence showing the benefits of NF, because there are no large, double-blind, placebo-controlled studies of NF, critics can argue that NF is only an effective placebo. But, because NF therapy, like psychotherapy, is usually very individualized and entails much clinician–patient interaction, a double-blind placebo-controlled study of NF is hard to envision—in that sense, NF is like a parachute for which there is scientific plausibility and evidence of efficacy, but a lack of double-blind, placebo-controlled studies.

This poster summarizes the history and basic methodology of NF, focusing on studies related to epilepsy, in order to bring NF to the attention of WCBR attendees unfamiliar with this exciting and rapidly-expanding area. The goal is to interest scientists and clinicians so that they will incorporate NF and some of the cutting-edge EEG-analytical techniques (real-time qEEG, LORETA, etc.) in their clinical or basic science investigations, thus yielding insights into mechanisms underlying clinical benefits seen with NF, as well as ideas for the design of studies to test NF, with the ultimate hope of better understanding the benefits and limitations of NF, in particular with regard to use in treating epilepsy.

P71 • Identifying novel LRRK2 substrates to elucidate the role of this kinase in Parkinson's disease pathophysiology

Warren Hirst, Gregory Luerman, Chuong Nguyen, John Dunlop*

Genetic mutations in Leucine Rich Repeat Kinase 2 (LRRK2) have been linked to a form of autosomal dominant Parkinson's disease (PD). One of the most prevalent mutations, the G2019S mutation, results in increased LRRK2 kinase activity which is believed to play a major role in the etiology of PD. Consequently, disease progression is likely mediated by phosphorylation-dependent LRRK2 substrate pathways. However, the endogenous substrates for LRRK2

are unknown. We performed a stable isotope labeling by amino acids in cell culture (SILAC)/mass spectrometry-based proteomic screen to identify changes in phosphoprotein expression upon acute treatment with a pharmacological LRRK2 kinase inhibitor. By identifying phosphoproteins and signaling pathways associated with LRRK2 kinase activity, we hope to elucidate those mechanisms implicated in Parkinson's disease as well as establish cellular-based activity models for inhibitor testing. This strategy identified and quantified phosphoprotein expression changes upon treatment of SH-SY5Y neuroblastoma cells, overexpressing a constitutively kinase-active LRRK2 mutant (G2019S), with a LRRK2 kinase inhibitor. Over 600 phosphopeptides were differentially regulated at least 1.5-fold in response to LRRK2 kinase inhibition, including proteins previously known to associate with LRRK2. The most down-regulated phosphoprotein was identified as the developmentally-regulated actin-binding protein, drebrin. We determined a cellular role for LRRK2 in the maintenance of drebrin expression and localization in primary neuron cultures. Additional validation came from BAC-transgenic LRRK2 mice and LRRK2 knockout mice. These data suggest that LRRK2 kinase activity may regulate key signaling pathways, including PKC signaling, stress kinases (MAPK/ERK/JNK), and actin dynamics. The regulation of drebrin by LRRK2 suggests a previously undefined link between LRRK2 activity and neuronal spinal morphogenesis and plasticity.

P72 • Anesthesia alters local field potential avalanches in rat visual cortex in vivo

Anthony Hudetz, Jeannette Vizuite, Siveshigan Pillay, Dietmar Plenzer*

Spontaneous neuronal activity in the cerebral cortex is characterized by bursts of population activity forming clusters called neuronal avalanches, whose size is statistically distributed according to power law with an exponent near -1.5 that purportedly maximizes neuronal information capacity (state of criticality). Neuronal avalanches have been found in slice cultures and wakeful animals, but the effects of general anesthesia on avalanche dynamics and information capacity in vivo have not been investigated. Local field potentials (LFP) in primary visual cortex at multiple depths were measured with chronically implanted multielectrode arrays in unrestrained rats at wakefulness and three levels of desflurane anesthesia corresponding to light to moderate sedation and unconsciousness (2%–6% inhaled concentration). Negative LFP deflections (nLFP) exceeding a suitable threshold were determined after subtracting the mean LFP yielding individual deviations from the population mean. Information capacity was estimated by shuffle-corrected nLFP population entropy and complexity measures. The power law exponent α decreased moderately with increasing nLFP threshold in the range of -1 to -2 (mean: -1.43). Neuronal avalanches

occurred dominantly in the superficial cortex with larger nLFP cluster size, interaction entropy, and complexity. Anesthesia at 6% desflurane decreased cluster size (-56%), alpha (-1.5 to -2.5), entropy (-72%), and complexity (-42%). Cluster size, entropy, and complexity were larger with than without subtraction of the mean LFP at similar alpha (7.8-, 3.4-, and 7.5-fold difference, respectively). In conclusion, moderate depths of anesthesia produces graded departure of neuronal network activity from criticality implying decreased information-processing capacity and complexity; the latter may be linked to loss of consciousness under anesthesia. Measuring nLFP deviations from the population mean improves the estimation of neuronal information capacity.

P73 • Dopamine oxidation facilitates rotenone-dependent potentiation of NMDA currents in rat substantia nigra dopamine neurons

Steven Johnson, Yan-Na Wu*

Rotenone is a mitochondrial poison that causes dopamine cell death and is used as a model of Parkinson's disease in rodents. Recently, we showed that rotenone augments currents evoked by N-methyl-D-aspartate (NMDA) by relieving voltage-dependent Mg^{2+} block in rat substantia nigra compacta (SNC) dopamine neurons. Because rotenone is well known to generate reactive oxygen species (ROS), we conducted the present experiments to evaluate the role of ROS in mediating the effect of rotenone on NMDA current augmentation. Using patch pipettes to record whole-cell currents from SNC neurons in slices of rat brain, we found that the ability of rotenone (100 nM) to increase NMDA (3–30 μM) current was antagonized by the antioxidant agent N-acetylcysteine (1 mM). In contrast, mercaptosuccinate (1 mM), which blocks glutathione peroxidase and raises tissue levels of H_2O_2 , mimicked rotenone by augmenting inward currents evoked by NMDA. Because oxidation of dopamine can also generate ROS, we explored the role of dopamine on this action of rotenone. We prepared dopamine-depleted midbrain slices from rats that had been pretreated with reserpine (5 mg/kg ip) and alpha-methyl-para-tyrosine (AMPT, 250 mg/kg ip). Dopamine depletion blocked the ability of rotenone (100 nM) to increase inward current evoked by NMDA (30 μM). Rotenone-dependent augmentation of NMDA current was also blocked by the monoamine oxidase inhibitor pargyline (100 μM) in slices prepared from normal rats. In contrast, the dopamine precursor levodopa potentiated the action of rotenone on NMDA current. These results suggest that ROS and/or dopamine oxidation products mediate the ability of rotenone to potentiate NMDA currents. Because excessive NMDA receptor stimulation can produce excitotoxicity, our results suggest that oxidative metabolism of dopamine might facilitate the neurotoxicity of rotenone.

P74 • Molecular determinants for subtype-selective ion channel block of NMDA receptors by argiotoxin analogs

Anders Kristensen, Mette Poulsen, Christel Jensen, Jacob Andersen, Kasper Hansen, Kristian Stromgaard*

The NMDA-type of ionotropic glutamate receptors (iGluRs) are involved in excitatory transmission in the mammalian brain and in a range of neurological and psychiatric diseases for which NMDA receptors are considered potential therapeutic drug targets. The majority of NMDA receptor subtypes are comprised of two glycine-binding GluN1 subunits and two glutamate-binding GluN2 subunits (NR2A-D); leading to the existence of four major receptor subtypes with distinct expression patterns and functional properties: GluN1/2A, GluN1/2B, GluN1/2C, and GluN1/2D. While the GluN1/2B subtype can be selectively inhibited by the highly subtype-selective noncompetitive antagonist ifenprodil, the lack of inhibitors with similar subtype-selectivity for the GluN1/2A, GluN1/2C, and GluN1/2D receptors is a limitation in studies exploring the role of these subtypes in many aspects of normal brain function and in disease. Polyamine toxins isolated from the venom of spiders are open-channel blockers of ion channels, in particular iGluRs. Argiotoxin-636 (ArgTX-636) from the orb weaver spider *Argiope lobata* consists of an aromatic amino acid head-group coupled to a polyamine tail. ArgTX-636 is a potent inhibitor of mammalian iGluRs; presumably by binding to the ion channel region of the receptors in a use- and voltage-dependent manner that blocks ion permeation. We have recently shown that modifications within the polyamine tail of ArgTX-636 can control selectivity between the NMDA- and the AMPA-type of iGluRs. Further exploration of our lead structures have led to the development of a series of ArgTX-636 analogs with selectivity towards GluN1/2A and GluN1/2B over GluN1/2C and GluN1/2D subtypes of NMDA receptors. In the present study, we have explored the molecular determinants underlying subtype-selectivity of ArgTX analogs using electrophysiological characterization of chimeric and mutant GluN1/2A and GluN1/2D NMDA receptors.

P75 • Right hemisphere dominance of ERP responses to voice auditory feedback in singers with perfect pitch

Charles Larson, Nadine Ibrahim, Roozbeh Behroozmand, Oleg Korzyukiv*

The pitch-shift technique has been successfully used in recent years to study the neural mechanisms underlying the role of auditory feedback on voice control. Most studies have been done on normal participants without extensive training in music. To further our understanding of the neural mechanisms

of voice control, the present study compared vocal and ERP responses to perturbations in voice auditory feedback in singers with and without “perfect pitch” ability. It has been previously shown using fMRI techniques that singers with perfect pitch have greater left hemisphere involvement while listening to variations in musical tones as compared with singers without perfect pitch ability. The present study tested the hypothesis that singers with perfect pitch would demonstrate greater left hemisphere neural activity in response to voice pitch-shifted auditory feedback. Event-related potentials (ERPs) were recorded in thirty-four singers (11 perfect pitch, 12 relative pitch, and 11 untrained nonmusicians) while they sustained vowel sounds (ah) and their voice pitch feedback was shifted up or down (100 cents, 200 ms duration) in a randomized sequence. Results showed that the amplitude of the P200 ERP component was significantly larger for the singers with perfect pitch compared to the other two groups. Topographic scalp distributions showed that there was a right hemisphere dominance of the P200 response (200–250 ms peak) in the nonmusicians and singers without perfect pitch. Singers with perfect pitch showed significantly larger ERPs in the left hemisphere compared to the other two groups. These findings support previous results of bilateral activations in singers with perfect pitch. The P200 ERP response may serve as an index of neural mechanisms related to musicality.

P76 • NGF precursor protein is elevated in CSF following acute spinal cord injury: Improving detection of therapeutic targets

Matthew Light, Kenneth Minor, Kyle Jasper, Jeannette Davies, Stephen Davies*

Background: A variety of methods have been used to study inflammatory changes in the acutely injured spinal cord. Recently novel multiplex assays have been used in an attempt to overcome limitations in numbers of available targets studied in a single experiment. Other technical challenges in developing pre-clinical rodent models to investigate biomarkers in CSF include relatively small volumes of sample and low concentrations of target proteins. Methods: A 34 cytokine sandwich ELISA microarray was used to study inflammatory changes in cerebrospinal fluid samples taken 12 days post-cervical spinal cord injury in adult rats. Results: We report a novel sub-acute SCI biomarker, elevated levels of MMP-8 protein in CSF, and discuss application of statistical models designed for multiplex testing. Conclusions: Major advantages of this assay over conventional methods include high-throughput format, good sensitivity, and reduced sample consumption. This method can be useful in creating comprehensive inflammatory profiles, and in the clinic, using biomarkers to assess injury severity and objectively grade response to therapy.

P77 • The genetic signatures of transposable elements (TE) in schizophrenia

Fabio Macciardi, Emanuele Osimo, Marquis Vawter, Federica Torri, Bernard Lerer, Simona Gaudi, Steven Potkin*

Introduction: Understanding how the information in the human genome is utilized is one of the central questions to unravel the genetics of complex diseases. Once completed, the human genome sequence has revealed being composed by transposable elements (TE) for about 45% and by coding genes in only 2%. Many genome-wide association studies (GWAS) in complex diseases have mapped disease-associated variations to noncoding regions, presumably regulatory and endogenous retroviral. TEs contain information that leads to editing, splicing, recombining, and mobilizing nucleic acid sequences in our complex human genome and play an important role in generating interindividual structural variation. Our aim is to identify and detect the expression levels of TEs in blood and brain samples from schizophrenia patients and matched controls. Methods: Our aim is to investigate the functional relationship between TE-related sequences and genes identified as “best” candidates via SNP mapping in genome wide association studies (GWAS) of schizophrenia. We also extend our analyses to Transcriptional Start Sites (TSS) for the same genes. These analyses are then complemented with target-resequencing of the entire genomic area, to look for differences between subjects who do or do not present the associated risk SNPs. Results and conclusion: For a prototypal gene, AHI1 (Torri et al, 2010) we found an excess of Alu, Line1 and Line2 elements across the AHI1 genomic region, with a clear pattern of tissue-specific expression that looks regulated by CNS-specific TSS. Initial sequencing in extreme subjects with and without the AHI1 risk haplotype show marked differences in their respective sequences. Our results strongly suggest that a detailed analysis of risk genes in complex disorders must include TE distribution and expression, and that it is perhaps only through inclusion of these elements that psychiatric diseases will be fully understood.

P78 • Analysis of neurogenesis in the postembryonic hypothalamus of zebrafish

Adam McPherson, Richard Dorsky*

Adult neurogenesis has been studied for some time in the mammalian dentate gyrus (DG) and rostral migratory stream (RMS), as an important element of behavioral plasticity. However, several other areas of the adult brain have been shown to possess neurogenic ability, yet the function of this neurogenesis is still unclear. The hypothalamus, which regulates homeostatic conditions throughout the body, is a region of the brain that has been shown to undergo postembryonic neurogenesis; however, it is unknown whether continual neurogenesis is

necessary for its proper output. In zebrafish, we have found that a population of GABAergic precursors intermingled within the feeding circuitry continues to produce neurons throughout the entire life of the fish. In mice, it has been shown that GABAergic interneurons in the feeding circuitry are necessary for maintaining proper body weight and lean-to-fat-mass ratios. We are testing whether the postembryonic generation of these cells is necessary for regulating feeding behavior and metabolic properties. The zebrafish allows us to take rapid and unique genetic and behavioral approaches to answer this question. We have developed transgenic animals in which we can label and kill these GABAergic precursors and are currently working to determine how these cells are born, integrated into the circuit, and ultimately what function this serves.

P79 • Analysis of dopamine D2 receptor mutants deficient in Arrestin3 binding using bioluminescence resonance energy transfer

Kim Neve, Cecilea Clayton*

Arrestins mediate dopamine D2 receptor internalization, desensitization, and regulation of signaling proteins such as Akt and GSK3beta. Furthermore, D2 receptor activation of arrestin-dependent signaling cascades is an important mediator of dopaminergic behaviors. We previously identified lysine 149 (K149) and amino acids 212-215 (IYIV) in intracellular loops two and three of the D2 receptor, respectively, as important for the interaction between arrestin3 and the receptor. Using bioluminescence resonance energy transfer (BRET) to measure receptor-mediated recruitment of arrestin, our objective was to determine the smallest mutation that prevents arrestin binding while retaining signaling through G-proteins. In contrast to our results using a different method to measure recruitment of arrestin to the plasma membrane, D2-K149C displayed arrestin recruitment and receptor internalization in response to quinpirole stimulation that was indistinguishable from the wild type receptor. Mutation of four residues within intracellular loop three (212-215, IYIV) abolished arrestin recruitment, but also impaired receptor expression. Mutation of three (213-215, YIV) or two (214-215, IV) residues reduced arrestin recruitment by forty and thirty percent respectively, without impairing receptor expression. Interestingly, mutating either four or three residues rendered the receptor incapable of agonist-induced internalization while sparing the receptor's ability to signal through G proteins. Thus, mutation of the sequence YIV213-215 at the N-terminus of IC3 of the D2 receptor selectively impaired arrestin recruitment and abolished arrestin-mediated internalization in HEK293 cells, suggesting that this mutant will be a useful tool for elucidating cellular and behavioral effects of D2 receptor stimulation that are mediated by arrestins.

P80 • Partial methamphetamine-induced striatal dopamine loss causes a change in circuitry mediating Arc-regulated response reversal learning

Elissa Pastuzyn, Kristen Keefe*

Methamphetamine (METH) causes partial loss of dopamine (DA) in the caudate/putamen in humans and rodents, and this loss has long-term detrimental effects on cognitive function. We have previously shown that the positive correlation between expression of the immediate-early gene Arc in dorsomedial (DM) striatum and learning on a motor response reversal task is lost in rats with METH-induced striatal DA loss, despite normal behavioral performance. This discrepancy suggests that METH-pretreated rats may no longer be using DM striatum to perform reversal. When saline (SAL)-pretreated rats are infused in DM striatum with either the NMDA receptor antagonist AP5 or with an Arc antisense oligonucleotide to knock down Arc expression, reversal learning or retention of learning, respectively, is impaired. However, METH-pretreated rats were unaffected by either compound. These data provide evidence that METH-pretreated rats do not use DM striatum to perform a normally striatally-mediated task. The logical next step is to determine which brain region/circuitry now mediates response reversal learning in these rats. Rats were pretreated with a neurotoxic regimen of (\pm)-METH (4x10 mg/kg, s.c., at 2-hr intervals) or SAL. Three weeks after METH, both groups were trained on a motor response acquisition task on a T-maze, and then underwent reversal. To analyze Arc expression in the brain, rats were sacrificed five minutes after reaching criterion on the reversal task. METH- and SAL-pretreated rats did not differ on number of trials required to reach criterion during reversal, as previously found. Arc expression is being examined via fluorescent and radioactive in situ hybridization in striatum, nucleus accumbens, prefrontal cortical areas, and hippocampus. Correlation between Arc expression and behavioral performance in any of these brain regions in METH-pretreated rats would implicate reliance on that brain region/circuitry instead of DM striatum in METH-pretreated rats on this task.

P81 • Zebrafish: An in vivo model for CNS axonal regeneration after injury

Jeffery Plunkett, Alexis Tapanes-Castillo, Fran Shabazz, Katarina Vajn, Martin Oudega*

It has been established in amphibians and fish that neurons can successfully regenerate their axons in the damaged central nervous system (CNS). This regenerative ability contrasts with that observed in mammals, whose neurons fail to regenerate their axon after CNS injury. Regeneration failure in the

mammalian CNS is due in part to the presence of axon growth-inhibitory molecules within and near the site of damage. These inhibitors ultimately prevent the formation of axon circuits that could be involved in or recruited for motor functions thereby facilitating functional restoration. We have previously demonstrated that chondroitin sulfate proteoglycans (CSPGs), a family of axon growth-inhibitory molecules are present following CNS injury in adult zebrafish. We then investigated whether a CSPG family member neurocan, which has been shown to play a role in the prevention of CNS regeneration in mammals, is found within injured adult zebrafish CNS. Using reverse transcription-polymerase chain reaction (RT-PCR), we now qualitatively demonstrate that neurocan and its putative receptor, receptor-type protein tyrosine phosphatase sigma a (ptprsa), are expressed in the CNS pre- and post-injury. Our overall objective is to understand the molecular mechanisms underlying the CSPG interactions of the regenerative neurons. We aim to generate data that may serve as a foundation for the development of tailored strategies to promote axon regeneration across injury sites in the spinal cord. (Funded by U.S. Dept. of Defense W81XWH-10-1-0617 to JAP.)

P82 • Orbitofrontal cortex is necessary when behavior is based on inferred but not cached values

Geoffrey Schoenbaum, Joshua L Jones, Guillermo Esber, Michael A McDannald, Alex Hernandez*

The orbitofrontal cortex has become closely associated with representation of value. Neural recording studies prominently feature activity that seems to reflect the general, common, or cached value expected in a particular situation, and orbitofrontal damage causes deficits in a variety of behaviors such as reversal learning, devaluation, and even transitivity that are commonly interpreted within a value framework. And yet most value-based behaviors do not require the orbitofrontal cortex, particularly when values have already been learned, or cached. And neural activity in the orbitofrontal cortex does not typically reflect value independent of the form and features of the outcome from which it is derived. This suggests that the orbitofrontal cortex might be critical to signaling value in some situations—for example, when value has to be derived through access to a representation of the expected outcome—and not in other situations—for example, when value can be determined accurately from prior training. Here, we tested this hypothesis directly using sensory preconditioning. Rats were first exposed to incidental pairings of several auditory cues (A→B; C→D). Subsequently, one of the auditory cues was paired directly with food reward (B→US), while a second cue was presented without reward (D).

Finally, in the critical probe test, each cue was presented after bilateral infusion of either saline or a baclofen/muscimol cocktail into the orbitofrontal cortex. We found that rats in both groups learned normally and responded strongly to the cue that had been paired directly with reward, B, in the probe test. In addition, saline-treated rats also showed high levels of conditioned responding to A, which was the cue that had been incidentally paired with B during preconditioning. Baclofen/muscimol-treated rats failed to respond to A. These results indicate that at the time a behavior must be executed, the orbitofrontal cortex is necessary when that behavior is based on inferred or model-based values but not when cached or model-free values are sufficient.

P83 • Sterotypic perseverative instrumental behavior associated with methamphetamine-induced neurotoxicity in rats

Jong-Hyun Son, James Kuhn, Kristen Keeffe*

Partial monoamine loss induced by methamphetamine (METH) is associated with impaired cognitive function in humans and rodents. Previously, we observed that such METH-induced neurotoxicity is associated with impaired formation of stimulus-response (S-R) associations underlying appetitive instrumental behavior. Furthermore, behavioral flexibility during instrumental training seemed to be affected in those animals. Thus, the present study examined whether METH-induced neurotoxicity is associated with alterations in behavioral flexibility. Rats were pretreated with (\pm) METH (4x10 mg/kg, s.c., 2-hr intervals) or saline. Starting 3 weeks after the treatment, rats were trained for 2 days (30 min/day, twice) using an FR1 schedule on an appetitive instrumental learning task requiring them to press a lever on one side of an operant chamber and then to retrieve reinforcer from a magazine on the opposite side. At the end of training, rats were sacrificed and brains removed for determination of striatal monoamine loss. Meth-pretreated rats with an ~50% loss of striatal DA made similar numbers of lever presses and head entries into the food magazine overall. However, more of these responses occurred during the wrong state; that is, METH-pretreated rats continued to make lever presses once the reinforcer was delivered and to make head entries into the magazine after the reinforcer was consumed. Accordingly, the latencies for METH-pretreated rats to switch between the lever and magazine were significantly longer. Thus, overall METH-pretreated rats earned fewer reinforcers. Taken together, these data suggest that METH-induced monoamine toxicity is associated with perseverative behavior on an appetitive instrumental learning task. (Supported by NIH grant DA024036.)

P84 • Primary neuronal brainstem culture from adult zebrafish: Interactions with an inhibitory chondroitin sulfate proteoglycan-rich environment

Alexis Tapanes-Castillo, Fran Shabazz, Katarina Vajn, Martin Oudega, Jeffery Plunkett*

Chondroitin sulfate proteoglycans (CSPGs) inhibit axonal regeneration from brainstem neurons in the injured mammalian spinal cord. In zebrafish, axons from brainstem neurons regenerate beyond a spinal cord injury site despite the presence of CSPGs. This ability is not characteristic of all brainstem neurons; different neuronal populations exhibit distinct responses, including failure to regenerate beyond the lesion site. To investigate the axonal growth response of zebrafish brainstem neurons to CSPGs, we developed a novel, primary neuronal culture system derived from the brainstem of adult zebrafish. We hypothesized that our culture would contain different neuronal populations that would respond distinctively to CSPGs in vitro. Our results support this hypothesis, revealing four different populations of brainstem neurons: (1) neurons repelled by CSPGs, (2) neurons that extend processes into CSPG areas, (3) neurons that grow axons exclusively on CSPGs, and (4) neurons that grow on CSPGs but extend processes out of the inhibitory environment. Our data suggest that the ability to grow across CSPGs is intrinsic to the neuron. We have molecularly characterized our heterotypic brainstem cultures using immunocytochemistry and found both neuronal and glial cell populations at various stages of differentiation. Finally, we are examining how growth-inhibiting molecules and growth-promoting molecules interact to regulate axon outgrowth in vitro. Our work focuses on the axonal growth-promoting zebrafish neuronal adhesion molecule L1.1 (nadl1.1), zebrafish neurocan, and receptor-type protein tyrosine phosphatase sigma a (ptprsa), a putative zebrafish CSPG receptor. (Funded by U.S. Dept. of Defense W81XWH-10-1-0617 to JAP.)

P85 • Mono- or polytherapy in the treatment of acute seizures and status epilepticus

Claude Wasterlain, Roger Baldwin, David Naylor, Kerry Thompson, Lucie Suchomelova, Jerome Niquet*

The reasons for preferring monotherapy in treating chronic epilepsy may not apply to status epilepticus (SE), a life-threatening event of limited duration. During SE, seizure-induced trafficking of synaptic GABA and glutamate receptors (R) reduces inhibition and increases excitation in hippocampus. Combination therapy aimed at correcting both changes may be more effective than monotherapy. Methods: We used a model of severe SE induced by high-

dose lithium and lipocarpine. Outcome measures were duration and severity of SE. Our treatment allosterically stimulated GABAAR with benzodiazepines. We added a drug which enhanced inhibition at a non-GABA site, since GABA agonists can only partially restore GABA inhibition in this model, and reduced glutamatergic excitation with NMDA antagonists. We administered treatment after benzodiazepine pharmacoresistance had developed. Results: Benzodiazepine monotherapy reduced mortality from 52% to 7% (5 mg/kg diazepam) or less (10–20 mg/kg) but did not stop seizures even at a dose of 20 mg/kg (Dz20), which induced coma (toxicity score 11.2 ± 0.9). The number of posttreatment seizures was 100 ± 7 in sham-injected controls and 100 ± 8 after 20 mg/kg DZ (N.S.). Monotherapy with ketamine 10 mg/kg (K), valproate 30 mg/kg (V), brivaracetam 10 mg/kg (Brv), diazepam (1, 5, or 10 mg/kg), and other drugs also failed to stop SE. Combinations of diazepam (1 mg/kg) with ketamine 10 mg/kg + valproate 30 mg/kg (Dz1 + K + V), reduced the number of posttreatment seizures to 8 ± 2 ($p < 0.001$ vs Dz or C) while preserving the righting reflex (toxicity score 1 ± 0.4). Some two-drug combinations were also effective. Synergism between drugs was strongly suggested by several methods. Significance: These results suggest that polytherapy can be more effective and less toxic than monotherapy in treating cholinergic SE, and that the optimal therapy of SE and acute seizures may be based on different principles than that of chronic epilepsy. (Supported by the Research Service of VHA, by grants NS13515, NS 05974, and NS074926 from NINDS, and by the James and Debbie Cho Foundation.)

P86 • Effect of mild traumatic brain injury (mTBI) on the hypothalamic-pituitary-adrenal axis feedback

Tao (John) Wu, Sibyl Swift, Stephen Shannon, David Carbone, John Skibo, Ozge Gunduz, Andrew Holmes, Robert Handa*

Following TBI there is over 30% incidence of patients exhibiting neuroendocrine dysfunctions often characterized by hypothalamic-pituitary-adrenal (HPA) axis dysregulation with ACTH or corticosterone (CORT) insufficiency and coincident behavior symptoms. HPA axis dysregulation often underlies neuropsychiatric disorders, including depression and anxiety. Nevertheless, there is a deficit in our understanding of the impact of mTBI on HPA axis function. Here, we utilized High Intensity Focused Ultrasound (HiFU), a new model of non-impact blast-induced TBI to examine the outcome of mTBI on HPA axis feedback. Adult male C57Bl/6 mice were subjected to mild HiFU exposure (400 mV for 1 ms, equivalent to 100 kPa). Animals were tested 24 h later to determine: (1) HPA axis (CORT) response to a 20-min immobilization stress, (2) Corticotrophin-releasing hormone (CRH), glucocorticoid receptor

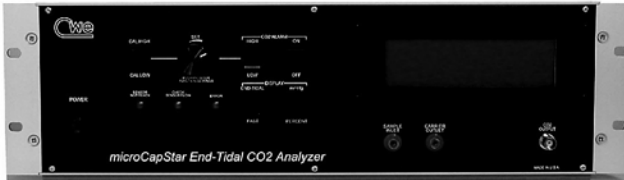
(GR), and (3) Fear-extinction behavior. While there were no changes in basal CORT, the CORT response to stress was attenuated ($p < 0.05$) in mTBI animals compared to sham controls when levels were examined at the end of the stressor (99.4 ± 5.0 ng/ml vs 110.0 ± 7.1 ng/ml, respectively) and 20 min after the end of the stress (75.8 ± 6.6 vs 98.1 ± 4.8 ng/ml, respectively). CORT was not different ($p > 0.05$) at later timepoints. CRH mRNA was not altered by mTBI in the paraventricular nucleus (PVN), but it was higher in the amygdala (AMG) of mTBI brains compared to sham. GR mRNA was lower in the PVN but greater in the AMG in TBI brains compared to shams. Fear conditioning revealed that both sham and mTBI mice increase ($p < 0.05$) freezing during conditioning ($65 \pm 11\%$ vs $73 \pm 1-6\%$, respectively); however, during extinction, levels of freezing remained elevated in mTBI mice ($68 \pm 4\%$) compared to shams ($38 \pm 9\%$) ($p < 0.05$). Thus, data suggest an impaired fear extinction pathway following mTBI. Overall, the results suggest a dysregulation of HPA axis feedback following mTBI leading to loss of fear extinction. (Funded by DMRDP, DoD.)





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