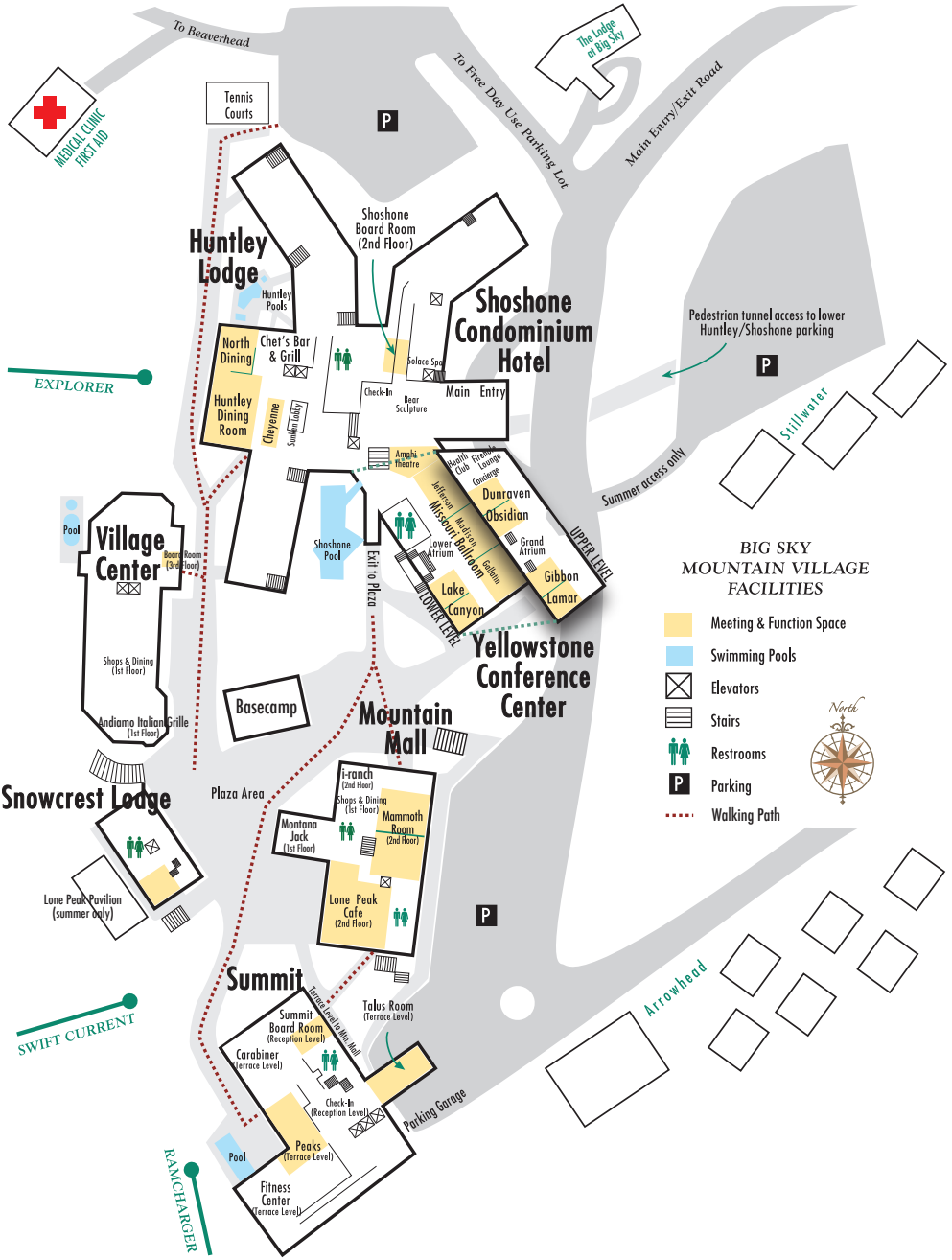
WINTER CONFERENCE ON BRAIN RESEARCH

BIG SKY, MONTANA
BIG SKY RESORT
JANUARY 25-30, 2020


To Beaverhead
MEDICAL CLINIC
FIRST AID
Tennis Courts
P
To Free Day Use Parking Lot
The Lodge at Big Sky
Main Entry/Exit Road
Huntley Lodge
Shoshone Board Room (2nd Floor)
Huntley Pools
North Dining
Chet's Bar & Grill
Huntley Dining Room
Cheyenne
Sundeck Lobby
Shoshone Condominium Hotel
Solace Spa
Check-In
Bear Sculpture
Main Entry
Pedestrian tunnel access to lower Huntley/Shoshone parking
EXPLORER
Amphitheatre
Health Club
Fireside Lounge
Concierge
Jefferson
Madison
Missouri Ballroom
Gallatin
Lower Atrium
Dunraven
Obsidian
Grand Atrium
UPPER LEVEL
Gibbon
Lamar
Lake
Canyon
LOWER LEVEL
Stillwater
Summer access only
Pool
Village Center
Board Room (3rd floor)
Shoshone Pool
Exit to Plaza
Shops & Dining (1st Floor)
Andiamo Italian Grille (1st Floor)
Basecamp
Mountain Mall
Yellowstone Conference Center
BIG SKY
MOUNTAIN VILLAGE
FACILITIES
Meeting & Function Space
Swimming Pools
Elevators
Stairs
Restrooms
Parking
Walking Path
North
Snowcrest Lodge
Plaza Area
i-ranch (2nd Floor)
Shops & Dining (1st Floor)
Montana Jack (1st Floor)
Mammoth Room (2nd Floor)
Lone Peak Cafe (2nd Floor)
Lone Peak Pavilion (summer only)
Summit
Summit Board Room (Reception Level)
Carabiner (Terrace Level)
Talus Room (Terrace Level)
Arrowhead
SWIFT CURRENT
Parking Garage
Check-In (Reception Level)
Peaks (Terrace Level)
Pool
Fitness Center (Terrace Level)
RAMCHARGER

WELCOME TO THE 2020 WINTER CONFERENCE ON BRAIN RESEARCH (WCBR).

This year is our 53rd annual meeting, and we are pleased to return to Big Sky, a favorite venue for excellent science and outstanding skiing. We are excited about the lineup of scientific and networking activities that will be offered during the conference. Please note that the conference is back to our usual schedule with the opening reception on Saturday, January 25, 2020 and the concluding banquet on Thursday, January 30, 2020.

The opening scientific presentation of the conference will be a plenary lecture during breakfast on Sunday, January 26th. Our speaker is Gregory W. Albers, MD, a Professor in the Department of Neurology and Neurological Sciences, and the Department of Neurosurgery at the Stanford University School of Medicine. Dr. Albers is the director of the Stanford Stroke Center, a position he has held since co-founding the center in 1992. Dr. Albers is an internationally recognized scientist and clinician who has been a pioneer in the diagnosis, management, and prevention of ischemic stroke. Dr. Albers and his team use advanced imaging technology to expand the treatment window for ischemic stroke. He has been the principal investigator of all 3 DEFUSE studies, which were NIH-funded research projects that clarified the evolution of brain ischemia and led to extending the treatment window for stroke to 24 hours in 2018. A prolific and distinguished researcher, Dr. Albers has authored more than 450 articles on topics related to cerebrovascular disease in peer-reviewed journals. Dr. Albers will be lecturing on the revolution in the rapid diagnosis and treatment of ischemic stroke. Modern imaging techniques that provide visualization of the ischemic core and penumbra have made the stroke treatment window transparent, which allows therapy to be tailored based on individual characteristics of specific patients. These advances have led to unprecedented progress in the treatment of acute stroke. Based on precision medicine techniques, in 2018 a quadrupling of the treatment window for stroke therapy was extended from 6 to 24 hours for eligible patients.

Throughout the conference, parallel panel presentations and daily poster sessions will span the breadth of neuroscience. Additional elements of the program warrant your attention. There will be two career development sessions, the first on Sunday, January 26th and the second on Tuesday, January 28th. In memorial to one of the mainstays of WCBR, a special session will be held in honor of Conan Kornetsky on Sunday, January 26th. On Wednesday evening, a special poster session will showcase the highest ranked posters from junior investigators. Please note that the Mountain Lunch will be Wednesday, January 29th. Skiers and non-skiers should all join together at this festive gathering!

The conference is pleased to host our first Diversity and Inclusion Coffee Hour on Monday, January 27th at 2:30 pm. Please join Kyle Frantz and other members of the Board of Directors in this interactive event to promote participation in all aspects of WCBR, from presentations to travel fellowships to board membership for our increasingly diverse meeting attendees. Improving the diversity of our

attendees and leadership is a priority for WCBR as we move forward. As part of WCBR's commitment to diversity and fostering a welcoming and inclusive environment, we are pleased to host a special session on the evening of Monday, January 27th at 7:00 pm, "Improving the Climate in Scientific Disciplines".

Two WCBR "Pioneer" panels will take place during the meeting, honoring the work of some the most accomplished scientists who have been regular attendees and leaders of WCBR over the past several decades. These sessions will each feature one speaker who has regularly attended the conference for decades and whose research has had major impact in neuroscience, followed by two more-junior speakers from the same field. The 2020 Pioneers are Drs. Fritz Henn and Eliot Gardner. Dr. Henn has had a long and distinguished career in neuropsychiatry, and currently is a Professor at Cold Spring Harbor Laboratory as well as a Professor of Psychiatry at the Icahn School of Medicine at Mount Sinai. Dr. Henn has done seminal research combining imaging, animal studies, and genetics to understand the biological bases of depression and schizophrenia. Dr. Henn has had an outstanding career in academia, chairing a department of psychiatry, running a major international research center in Germany, and recently serving as the Associate Laboratory Director for Life Sciences for 4 years at the Brookhaven National Laboratory. Dr. Gardner is a Senior Investigator in the Molecular Targets and Medications Discovery Branch, Neuropsychopharmacology Section of NIDA. Dr. Gardner has been a leader in the study of addiction for several decades. He has conducted internationally recognized research directed toward the development of effective anti-addiction, anti-craving, anti-relapse medications. His work has centered around basic brain mechanisms underlying drug addiction, craving, and relapse, endocannabinoid brain mechanisms and addiction, dopamine D3 receptor antagonists, slow-onset long-acting dopamine transport inhibitors and drugs acting on the endocannabinoid brain system. Please join us in honoring these two Pioneers in neuroscience and active participation in WCBR.

The conference will also host outreach events for the local community including school visits and a "brain talk" town meeting open to the general public. This year's Brain Talk Town Hall will be a presentation from our plenary speaker Dr. Greg Albers, who will be discussing stroke prevention, diagnosis, and management for the lay public. The talk will be held on Monday, January 27th at 7:00pm.

An important aspect of WCBR is the abundant opportunity for networking, from the opening reception on Saturday night through to the banquet on Thursday evening. Big Sky has amazing skiing, along with multiple dining options, shopping, and other off-slope entertainment. It has extensive slopes for all levels, and plenty of activities for non-skiers. The West Gate to Yosemite National Park is within an hour's drive from Big Sky and offers an unparalleled experience of scenic beauty and wildlife in the winter. We are certain you will enjoy it.

Thomas M. Hyde, Conference Chair
53rd Winter Conference on Brain Research
Big Sky Montana, January 25-30, 2020

Contents

General Information

WCBR INFORMATION DESK AND MESSAGE CENTER are located at the Yellowstone Conference Center, Upper Atrium.

The Information Desk hours are as follows:

Saturday, January 25, 2020	12:00 p.m. – 7:00 p.m.
Sunday, January 26, 2020	7:00 a.m. – 7:30 p.m.
Monday, January 27, 2020	7:00 a.m. – 7:30 p.m.
Tuesday, January 28, 2020	7:00 a.m. – 7:30 p.m.
Wednesday, January 29, 2020	7:00 a.m. – 10:00 a.m. & 3:00 p.m. – 6:00 p.m.
Thursday, January 30, 2020	7:00 a.m. – 6:00 p.m.

Pick up your badge at the WCBR Information Desk in the Yellowstone Conference Center, Upper Atrium. Any additional items purchased (such as guest meal tickets, printed program book, etc.) will also be available at registration.

Exhibits and Poster Sessions are in Jefferson and Madison. Light refreshments are provided from 3:30 p.m. – 4:30 p.m., Sunday, January 26th through Wednesday, January 29th. Exhibitor setup is Sunday, January 26th, from 12:00 p.m. – 3:00 p.m. All exhibitors should have their materials removed by 10:00 p.m. on Wednesday, January 29th.

POSTER SESSION 1, SUNDAY, JANUARY 26th
Posters can be set up after 11:30 a.m. on Sunday.

Posters will be available for viewing from 12:00 p.m. – 7:00 p.m. on Sunday. Presenters will be at their posters from 3:30 p.m. – 4:30 p.m. Posters must be removed by 8:30 p.m. on Sunday.

POSTER SESSION 2, MONDAY, JANUARY 27th
Posters must be set up between 8:00 a.m. – 11:30 a.m. on Monday.

Posters will be available for viewing from 12:00 p.m. – 7:00 p.m. on Monday. Presenters will be at their posters from 3:30 p.m. – 4:30 p.m. Posters must be removed by 8:30 p.m. on Monday.

POSTER SESSION 3, TUESDAY, JANUARY 28th
Posters must be set up between 8:00 a.m. – 11:30 a.m. on Tuesday.

Posters will be available for viewing from 12:00 p.m. – 7:00 p.m. on Tuesday. Presenters will be at their posters from 3:30 p.m. – 4:30 p.m. Posters must be removed by 8:30 p.m. on Tuesday.

POSTER SESSION 4, WEDNESDAY, JANUARY 29th
Posters must be set up between 8:00 a.m. – 11:30 a.m. on Wednesday.

This is a special session displaying the highest-ranked posters by young investigators. A grand prize and several other prizes will be presented to the best posters. Presenters will be at their posters from 3:30 p.m. – 4:30 p.m. and return for the special session from 7:30 p.m. – 9:30 p.m. Posters must be removed by 10:00 p.m. on Wednesday.

Please refer to pages 31–38 for a listing of poster sessions.

BREAKFAST is served to all conference delegates during the keynote presentation on Sunday, January 26th from 7:00 a.m. – 8:30 a.m. in the Missouri Ballroom. Tickets are not required for the Sunday breakfast.

Monday through Thursday breakfast will be available from 6:30 a.m. – 10:30 a.m., in Huntley Dining Room & Peaks Restaurant (Summit Hotel).

Don't forget to visit the posters & exhibits

Continuing Medical Education (CME)

SATISFACTORY COMPLETION

Learners must complete an evaluation form to receive a certificate of completion. Your chosen sessions must be attended in their entirety. Partial credit of individual sessions is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

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In support of improving patient care, this activity has been planned and implemented by Amedco LLC and the Winter Conference on Brain Research (WCBR). Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Credit Designation Statement – Amedco LLC designates this live activity for a maximum of 30.5 *AMA PRA Category 1 Credits™* for physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Don't forget to visit the posters & exhibits

Conference Support

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The Winter Conference on Brain Research and Amedco would like to acknowledge the generosity of the companies and institutions listed below whose unrestricted educational grants have contributed to the overall quality of this meeting.

Supernus Pharmaceuticals

The National Institute on Drug Abuse and the National Institute on Alcohol and Alcoholism of the National Institutes of Health under Award Number R13 DA047792.
The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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The Winter Conference on Brain Research appreciates the generous contribution of our Corporate Supporters.

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Pioneer Awardees

For the 53rd WCBR meeting, we are honoring two scientists who have greatly contributed to the field of neuroscience, as well as to WCBR. These Pioneers will present their work during the special Pioneer Sessions on Sunday, January 26th and Tuesday, January 28th.

ELIOT L. GARDNER, PH.D.

Dr. Eliot L. Gardner was born and raised in Boston, and learned to ski at age 7 on local hills (wooden skis, bear-trap bindings, real old-school). Originally a mathematics major at Harvard College, he enrolled in a psychopharmacology course at Harvard Medical School in his junior year, and was captivated by the subject. He spent his last two years at Harvard learning psychopharmacology in depth – as a research assistant in the Psychopharmacology Research Unit, and making morning psychopharmacology rounds of patients with the senior members of the Unit. After receiving his A.B. from Harvard in 1962, he moved to Montreal to further his studies in psychopharmacology and neuroscience at McGill University, the Queen Elizabeth Hospital, the Royal Victoria Hospital, and the Montreal Neurological Institute. He received an M.A. degree from McGill in 1964, and a Ph.D. in 1966. From 1966 to 1969, he served as a medical research officer (Captain, Biomedical Sciences Corps) in the U.S. Air Force – serving as a branch chief at the U.S. Air Force School of Aerospace Medicine's enormous non-human primate research center at Alamogordo (White Sands), New Mexico. In 1969, he embarked upon a 2-year postdoctoral fellowship in pharmacology, followed by a second 2-year postdoctoral fellowship in neurology, at Albert Einstein College of Medicine in New York City. He was then offered a junior faculty appointment at Albert Einstein, and remained on faculty there for 33 years – in the Departments of Pharmacology, Neurology, Psychiatry, and Neuroscience. In 2000, he was recruited to the Intramural (in-house) Research Program at the National Institute on Drug Abuse of NIH, where he is Chief of the Neuropsychopharmacology Section in the Molecular Targets and Medications Discovery Research Branch.

Eliot has devoted his research career to studying brain reward mechanisms and the neurobiology of addiction. He was one of the first to propose that

dopamine is the essential neurotransmitter of the brain's principal reward pathway from ventral tegmental area to nucleus accumbens. He was also the first to show that delta-9-tetrahydrocannabinol activates brain reward mechanisms – deriving its addictive potential therefrom. And that highly selective cannabinoid CB1 antagonists and CB2 agonists have potent anti-addiction potential. He was also the first to show that highly selective dopamine D3 receptor antagonists have potent anti-addiction efficacy against a remarkably wide range of addictive substances in a remarkably wide range of preclinical animal models with arguably high translational relevance.

Eliot has received numerous awards and honors for his work – including the Newton Society Prize, Fellow of the American Psychological Association, Career Scientist Award of the Health Research Council of New York, Distinguished Basic Science Scholar for the Year 2000 by the American Academy of Addiction Psychiatry, and the NIH Director's Merit and Honor Awards.

Eliot has attended WCBR for more than 50 years – from its inception at the first 1968 meeting at Lake Tahoe. He has organized and participated in panels and workshops, and competed in the Smitty Stevens race (never matching Chuck O'Brien's times, an unfulfilled – and unrealistic – long-time desire). He has also participated in WCBR's local school outreach program, and in Brain Talk Town Meetings. When George Koob's son Cameron was 4 years old, Eliot put the young lad on skis for the first time at a WCBR meeting. Cameron now leaves George, Eliot, and virtually everyone else in his dust on the slopes. Eliot has exceptionally fond memories of skiing with Chuck O'Brien, Conan Kornetsky, Tom Crowley, Roy Wise, Dave Kline, Kyle Frantz, Bert Weiss, Fritz Henn, Jim McElligott, Bart Hoebel, and far too many others to mention. He treasures the friendships, networking, and research collaborations formed on the slopes and in the scientific sessions. He has also brought his students and postdocs to WCBR meetings, helping to foster new generations of attendees.

FRITZ HENN, M.D., PH.D.

Dr. Fritz Henn is a psychiatrist and neuroscientist and received his BA from Wesleyan University in1963, a PH.D. in biochemistry from Johns Hopkins University in 1967 and an MD from the University of Virginia in 1971. His postdoctoral training was at Washington University in Psychiatry and in Goteborg Sweden in neurobiology. His initial faculty appointment was at the University of Iowa in Psychiatry and he left as a full Professor to assume the chair in Psychiatry and Director of the Long Island Research Institute in 1980. He began attending WCBR while in Iowa and one

of his first experiences was to take some beautiful wooden cross country ski's to his first meeting at Keystone in the 70's and go with some experts from British Columbia to ski above Leadville where he developed mild pulmonary edema, they got him off the mountain and there was an uneventful recovery. After assuming the Chair at Stony Brook, Harvey Karten got him not only to attend regularly but to become involved on the board and at the 25th anniversary of the meeting he was President and led us to wet Whistler. Following Jill Becker down a trail at Whistler I ended up falling into a 6 ft tree hole which took work to get out of, I'm not sure she noticed. I really learned to ski at WCBR over the years often with Conan giving me tips. In 1977 as president I worked with Bill Greenough to move the meeting organization from the group which had founded the meeting at UCLA into a University affiliated meeting with the U. of Illinois. This was a difficult transition but appears to have been the right one for WCBR.

Dr. Henn's work beginning in Iowa was centered understanding depression and on defining to role of astrocytes. An early PNAS paper was the basis for the idea of a tripartite synapse, with astrocytes playing a role in glutamate transmitter uptake and recycling back to neurons. Following this work he focused on understanding depression using the animal model learned helplessness. In 1994 he made the decision to leave Stony Brook and accepted the Directorship of the Central Institute of Mental Health (ZI) and a Professorship at Heidelberg Germany. ZI became the leading psychiatric research center in Germany and initiated the first substance abuse program in a University, under much protest. Here both Chuck Obrien and Nora Volkow were invaluable. The work on learned helplessness progressed with the development of inbred helpless and non helpless lines. This lead to a new circuit being proposed for depression involving the l. habenula. This work was done after his return to the United States at Brookhaven National Lab and later at Cold Spring Harbor Lab. The circuit has been tested in cases of intractable depression and although the DBS target is a very difficult target patients who failed all treatment including ECT have responded. Dr. Henn is a member of the German Academy of Science and received the Distinguished Service Cross of Germany upon his retirement there. He is a fellow of the AAAS in neuroscience and was a Professor at CSHL and Mt. Sinai until his retirement from lab work 2 years ago. The clinical studies of DBS are ongoing at Baylor with Dr. Gooden.

Featured Presenter

GREGORY ALBERS, M.D.

Gregory Albers, M.D., Director of the Stanford Stroke Center, will be the 2020 Keynote and Brain Talk Town Hall presenter. Dr. Albers' research focus is the acute treatment and prevention of cerebrovascular disorders. He and his group's primary interest is the use of advanced imaging techniques to expand the treatment window for ischemic stroke. They are also conducting clinical studies of both neuroprotective and thrombolytic strategies for the treatment of acute stroke and investigating new antithrombotic strategies for stroke prevention.

KEYNOTE

Sunday, January 26, 2020 from 8:30 a.m. – 9:30 a.m.

How the Stroke Stopwatch was Shattered

Missouri Ballroom

BRAIN TALK TOWN HALL

Monday, January 27, 2020 from 7:00 p.m. – 8:30 p.m.

The Transparent Time Window: A New Perspective on Stroke Treatment

Talus Room

Winter Conference on Brain Research Policy Information

CODE OF CONDUCT

1. Introduction

The Winter Conference on Brain Research (WCBR) is dedicated to providing a safe, productive and discrimination-free experience for all participants during the Annual Meeting regardless of race, color, national origin, religion, creed, age, sex (including pregnancy), gender, gender identity, physical or mental disability, perceived disability, ancestry, marital status, genetic information, sexual orientation, citizenship, past, current or prospective service in the uniformed services, or any other basis protected by federal, state or local laws. WCBR does not tolerate discrimination or any form of harassment and is committed to enforcing this Code of Conduct Policy. As a professional society, the WCBR is committed to providing an atmosphere that encourages the free expression and exchange of scientific and educational ideas. Furthermore, WCBR upholds the philosophy of equality of opportunity for, and treatment of, all meeting participants, including but not limited to, attendees, guests, speakers, exhibitors, contractors, staff, and volunteers at all venues and events, including all ancillary and unofficial social events held in conjunction with the Annual Meeting (collectively "Annual Meeting").

2. Scope of Code of Conduct

WCBR seeks to create a diverse, inclusive and respectful environment for the exchange of scientific information.

WCBR requires compliance with this Policy by all meeting participants throughout the period of the Annual Meeting, whether in public or private facilities. This policy is an expression of WCBR's values and commitment to a safe and productive experience for all participants at the Annual Meeting. This policy is not an acknowledgement, admission, or description of WCBR's legal obligations with respect to any of the subject matters addressed herein, nor does it create any such legal obligations on WCBR, its Board Members, and committee members.

3. Prohibited Conduct

Prohibited conduct at the WCBR Annual Meetings include, but is not limited to:

a. harassment and discrimination based on race, color, national origin, religion, creed, age, sex (including pregnancy), gender, gender identity, physical or mental disability, perceived disability, ancestry, marital status, genetic information, sexual orientation, citizenship, past, current or prospective service in the uniformed services, or any other basis protected by federal, state or local laws;

b. demeaning comments or harassment about a person's professional status, qualifications, or affiliations;

c. sexual harassment, as defined in Section 4;

d. abusive conduct that has the purpose or effect of unreasonably interfering with another person's ability to benefit from and enjoy or participate in the Annual Meeting;

e. undue or excessive interruption of any event, speaker, or session; and

f. violence or threats of violence or physical harm.

4. Harassment Defined

Prohibited harassment includes any conduct that creates an intimidating, offensive, or hostile environment whether that conduct be verbal, physical, or visual. Harassment can take many forms and includes, but is not limited to, the following: slurs, epithets, derogatory comments, insults, degrading or obscene words, jokes, demeaning statements, offensive gestures, or displaying derogatory or demeaning pictures, photos, drawings, or cartoons based upon an individual's race, color, national origin, religion, creed, age, sex, pregnancy, gender, gender identity, physical or mental disability, perceived disability, ancestry, marital status, genetic information, sexual orientation, citizenship, past, current or prospective service in the uniformed services, or any other basis protected by federal, state or local laws. Sexual harassment includes unwanted sexual attention including expressions of romantic or sexual interest that are unwelcome, unreciprocated, and/or offensive to the target; examples include unwanted touching, hugging, stroking, and persistent requests for dates or sexual behavior despite discouragement. Sexual harassment also includes gender harassment which includes verbal and nonverbal behaviors that convey insulting, hostile, and degrading attitudes about members of one gender as well as crude harassment.

Sexually harassing conduct can be by a person of either the same or other sex. Conduct that begins as consensual in nature may become harassment if one party withdraws his or her consent. Sexual or other harassment prohibited by this policy is unacceptable and will not be tolerated.

The above list of prohibited behaviors is not a complete rendering of what may be deemed sexual or other harassment prohibited by this policy. It is impossible to define every action or word that could be interpreted as harassment or discrimination. However, WCBR has a "zero tolerance" policy toward discrimination and all forms of harassment. WCBR reserves the right to discipline meeting participants who engage in any inappropriate conduct, even if it is not specifically referred to or defined in this Code of Conduct, or is not legally actionable as sexual or any other form of harassment.

5. Filing a Formal Complaint

If you feel you have been subject to or have witnessed a violation of this Code of Conduct, a formal complaint can be filed with an authorized representative from our meeting management company, Parthenon Management Group, LLC. This individual can be contacted through the registration desk, or if after the Annual Meeting, at 615-324-2365. No participant will be retaliated against for making a good faith claim of harassment or discrimination, for opposing harassment or discrimination, or for participating in, or cooperating with, the investigation of a complaint. A designated member of the Parthenon team will gather information and put together a summary

report, which will then be forwarded to the Conduct Subcommittee of the Executive Board of WCBR for a decision. If the decision of the Subcommittee is contested, it can be appealed to the full Executive Board. The decision following appeal is final and not subject to further appeal. We will strive to keep the identity of the complainant and any witnesses, as well as the accused individual, confidential throughout this process. All participants of the Annual Meeting are bound by the decisions of the Conduct Subcommittee of the Executive Board. If it is determined that an individual has engaged in conduct constituting harassment or discrimination, discipline may be imposed, up to and including exclusion from participating in the WCBR Annual Meeting, and/or future meetings.

Code of Conduct Attestation:

The WCBR Annual Meeting is committed to supporting discovery and scientific dialogue, and providing an atmosphere that is safe, respectful and welcoming to all those present in order to encourage the free expression and exchange of scientific and educational ideas. This commitment applies to the WCBR Annual Meeting, at all venues and events, including all ancillary and unofficial social events held in conjunction with the Annual Meeting (collectively "Annual Meeting") and anyone present, including but not limited to, attendees, guests, speakers, exhibitors, contractors, staff, and volunteers.

To that end, the WCBR Annual Meeting strictly prohibits and does not tolerate unlawful harassment or discrimination on the basis of race, color, religion, creed, national origin, ancestry, sex (including pregnancy), sexual orientation, gender (including nonconformity and status as a transgender or transsexual individual), gender identity, age, physical or mental disability, perceived disability, citizenship, marital status, genetic information, past, current or prospective service in the uniformed services, or any other basis recognized by applicable federal, state, or local laws. WCBR upholds the philosophy of equality of opportunity for, and treatment of, all individuals present at the Annual Meeting and thus, does not tolerate any form of discrimination, harassment, and/or retaliation. We expect all those present at the Annual Meeting of the WCBR to help us in ensuring a productive, safe and positive environment for all.

By registering for the meeting, I confirm that I have read the Code of Conduct for the WCBR, and agree that it is my responsibility to be familiar with, and to abide by, its terms. I also attest that I will cooperate with any formal or informal inquiry into my behavior and/or actions at the Annual Meeting. I agree to be bound by the decisions of the Executive Subcommittee on Meeting Conduct, which may take any action that it deems appropriate, including but not limited to exclusion from a current Annual Meeting (without refund) or from future meeting.

PHOTOGRAPHY AND VIDEOGRAPHY POLICY

WCBR does not allow photography or videography of oral presentations, slides and/or posters without permission from the presenter. At the beginning of the presentation, the presenter must either grant permission to the audience and/or include an icon on the first slide or poster signifying photos or videos are allowed.

Program

SATURDAY, JANUARY 25, 2020

6:00 P.M. - 6:30 P.M.

Welcome Reception for Newcomers, Travel Fellows, and Mentors • Huntley Dining Room

6:30 P.M. - 7:30 P.M.

Welcome Reception (All are welcome!) • Jefferson/Madison

SUNDAY, JANUARY 26, 2020

7:00 A.M. - 8:30 A.M.

Breakfast • Missouri Ballroom

8:30 A.M. - 9:30 A.M.

Plenary • Missouri Ballroom

How the Stroke Stopwatch was Shattered

Gregory Albers

9:45 A.M. - 11:00 A.M.

Pioneer Session # 1: Fritz Henn • Amphitheater

Understanding the Neurobiological Basis of Depression

Pioneer: Fritz Henn
Chair: Lloyd Fricker
Investigators: Bo Li, Alexander Sartorius

12:30 P.M. - 2:00 P.M.

Special Session • Dunraven/Obsidian

Conan Kornetsky's Memorial Panel

Jacqueline McGinty (Chair), George Koob, Linda Porrino, Chris Pierce, David Root

2:00 P.M. - 3:30 P.M.

Career Development Session # 1 • Cheyenne

NIH Grant Application & Reviews

Brad Cooke (Chair), David Devilbiss, Lakshmi Devi, Gretchen Snyder, Paul Phillips, Dana Plude

3:30 P.M. - 4:30 P.M.

Exhibits & Poster Session I • Jefferson/Madison

4:30 P.M. - 6:30 P.M.

Panel • Amphitheater

Contribution of Glia to Brain Function and Disorders

Yongjie Yang, Martin Paukert (Co-Chair), Long-Jun Wu, Hye Young Lee (Chair)

Panel • Canyon

Neuroendocrine and Neuroimmune Modulation in Stress and Addiction

Dean Kirson (Co-Chair), Zoe McElligott, Kelly Cosgrove, Carolina Haass-Koffler (Chair)

Panel • Cheyenne

Kratom –Potential Drug of Abuse or Useful Analgesic Without Opioid-Like Side-Effects?

Daniel Morgan (Chair), Christopher McCurdy, Abhisheak Sharma, Lance McMahon, Jenny Wilkerson (Co-Chair)

Panel • Dunraven/Obsidian

Frontal Cortical Regulation of Motivated Behaviors

Evan Hart, Cody Siciliano (Co-Chair), Christina Gremel, Vijay Mohan K. Namboodiri (Chair)

Panel • Gallatin

Neural Systems Mediating Passive and Active Responses During Aversive Situations

Lindsay Halladay, Mahsa Moaddab, Maria Diehl, Matthew Wanat (Chair)

Panel • Gibbon

New Treatment Strategies for Mood Disorders: From IBT to ECT

Anna Van Meter, Anil Malhotra (Chair), Daphne Voineskos, Miklos Argyelan

Panel • Lake

Synaptic Transmission and Plasticity Regulated by Neurotransmitter Receptor Auxiliary Subunits

Yael Stern-Bach, Andres Maricq, David Bredt (Chair), Wei Lu

Panel • Lamar

New Approaches to Treating Patients in Status Epilepticus

Thomas Bleck, Hilary McCarren, Claude Wasterlain, Denson Fujikawa (Chair)

6:30 P.M. - 7:00 P.M.

Refreshment Break • Upper Atrium

7:00 P.M. - 8:30 P.M.

Panel • Amphitheater

Pain and Itch: How are They Motivating You?

Paul Phillips (Chair), Tamara Markovic, Amber Alhadeff, Tayler Sheahan

Panel • Canyon

Viral Vectors for Gene Modifications to Enable Axon Regeneration

Kevin Park, Binhai Zheng, Oswald Steward (Chair)

Panel • Cheyenne

It's Not All Dopamine: The Role of Serotonin in the Regulation of Impulsive Behavior

Catharine Winstanley, Noelle Anastasio, Katherine Nautiyal (Chair)

Panel • Dunraven/Obsidian

Long-Term Behavioral and Neurobiological Effects of Adolescent Drug Use

Elizabeth Pitts (Chair), Anushree Karkhanis, Mary Torregrossa

Panel • Gallatin

Cholinergic Modulation Shapes Striatal Microcircuitry: Roles in Reinforcement Learning and Reward-Seeking Behavior

David Lovinger, Kate Wassum, Samantha Yohn (Chair), Mark Ferris

Panel • Gibbon

Investigating Brain Circuits in Neurodevelopmental Disability, From Molecular to Electrophysiological Aspects

Francois Bolduc (Chair), Sarah Lippe, Jean-Francois Lepage

Panel • Lake

Obesity Induced Changes to Brain Motivation Circuits

Richard O'Connor (Chair), Bridget Matikainen-Ankney, Morgan James

Panel • Lamar

Visual Circuit Function and Plasticity

Huizhong Tao (Chair), Jianhua Cang, Nicholas Priebe, Sandra Kuhlman, Hey-Kyoung Lee

MONDAY, JANUARY 27, 2020

6:30 A.M. - 8:30 A.M.

Board of Directors Meeting (Invitation Only) • Talus

6:30 A.M. - 8:30 A.M.

Breakfast at Leisure • Huntley Dining Room/Peaks Restaurant

7:30 A.M. - 9:30 A.M.

Panel • Amphitheater

Sex Differences in the Effects of Cannabis and Cannabinoid Signaling

Aimee McRae-Clark, Elise Weerts, Ryan McLaughlin (Chair), Matthew Hill

Panel • Canyon

Advancements in Psychedelic Neuroscience

David Martin (Chair), Natalie Hesselgrave, Cristopher Niell, Katrin Preller

Panel • Cheyenne

Fatal Fentanyl: How One Pill Can Kill

Terrence Boos, Irma Cisneros (Co-Chair), Kim Janda, Phil Skolnick (Chair)

Panel • Dunraven/Obsidian

From Clusters to Stroke Busters: The Cellular, Molecular and Translational Biology of Kv2.1/Neuregulin Complexes

Elias Aizenman (Chair), Michael Tamkun, Andres Buonanno, Robert Fyffe, Anthony Schulien

Panel • Gallatin

Molecular Adaptations Underlying Motivation and Drug-Associated Behaviors

Alberto Lopez (Chair), Megan Fox, Rianne Campbell (Co-Chair), Courtney Miller

Panel • Gibbon

Circuits and Functions of Neurons Defined by Multiple Genetic Characteristics

Marisela Morales (Co-Chair), Lief Fenno, Susana Mingote, Patricia Jensen, David Root (Chair)

Panel • Lake

Rhythms on the Slope

Kamran Diba (Chair), Lara Rangel, Amy Griffin, Andrew Maurer (Co-Chair), Carmen Varela

Panel • Lamar

Neuropeptide Signaling Mechanisms: From Molecules to Circuits to Behavior

Jenny He, Julia Lemos (Co-Chair), Alexa Veenema, William Giardino (Chair)

2:30 P.M. - 3:30 P.M.

Diversity and Inclusion Coffee Hour • Dunraven/Obsidian

3:30 P.M. - 4:30 P.M.

Exhibits & Poster Session II • Jefferson/Madison

4:30 P.M. - 6:30 P.M.

Panel • Amphitheater

Genetic In Vivo Models of Neurological Disease

Wayne Frankel, Stephen Traynelis (Chair), Geoffrey Swanson, Jennifer Kearney

Panel • Canyon

Striatal Interneurons: Orchestrating Synaptic and Behavioral Adaptations

Patrick Rothwell, Anne West, Brad Grueter (Chair), Brian Mathur

Panel • Cheyenne

Cannabinoids, Sleep and PTSD: A Bench to Clinic Primer

Andrew Kesner, Margaret Haney, Ryan Vandrey (Chair), Marcel Bonn-Miller

Short Course • Dunraven/Obsidian

Analysis, Visualization and Data Sharing for Human Intracranial Recording and Stimulation

Michael Beauchamp (Chair), Kai Miller, Dora Hermes, Dominique Duncan, John Magnotti,

Panel • Gallatin

It's all Downhill From Here: Dopamine Function and Dysfunction in Movement Initiation

Elyssa Margolis (Chair), Jakob Dreyer, Mark Howe, Alexandra Nelson, Leslie Sombers (Co-Chair)

Panel • Gibbon

Linking Endocytosis to Neuronal Survival

J. Marie Hardwick, Leonard Kaczmarek, Elizabeth Jonas (Chair), Zhenyu Yue

Panel • Lake

New Developments on Hypothalamic and Brainstem Control of Defensive Behaviors

Sung Han, Jaideep Bains, Jason Radley, Avishek Adhikari (Chair)

Panel • Lamar

Structural, Functional and Molecular Mechanisms of Dendritic Spine Plasticity

Yi Zuo (Chair), Kristen Harris, Ryohei Yasuda, Jason Shepherd

7:00 P.M. - 8:30 P.M.

Special Session • Amphitheater

Improving the Climate in Scientific Disciplines

Jill Becker (Chair), Kathryn Clancy, Paul Phillips, Jonathan Morrow, Carrie Ferrario

Brain Talk Town Meeting • Gallatin

The Transparent Time Window: A New Perspective on Stroke Treatment

Gregory Albers

9:00 P.M. - 11:00 P.M.

Karaoke • Montana Jack

TUESDAY, JANUARY 28, 2020

6:30 A.M. - 8:30 A.M.

Travel Fellow/Mentor Breakfast • Chet's

6:30 A.M. - 8:30 A.M.

Breakfast at Leisure • Huntley Dining Room/Peaks Restaurant

7:30 A.M. - 9:30 A.M.

Panel • Amphitheater

Broadening the Neural and Associative Mechanisms of Fear

Joshua Johansen, Melissa Sharpe (Chair), Stephen Maren, Moriel Zelikowsky

Panel • Canyon

Gene and Protein Networks in Autism and Schizophrenia

James Knowles, Dan Geschwind (Co-Chair), Stephen Smith (Chair), Lilia Iakoucheva

Panel • Cheyenne

Neurobiological Mechanisms Underlying the Potential Therapeutic Effects of Psychedelics

Melissa Herman (Chair), Mark Geyer, Samuel Slocum, William Wetsel, Harriet de Wit

Workshop • Dunraven/Obsidian

Educating the Next Generation: Innovative Approaches to Make Science Fun

Lloyd Fricker (Chair), Sybil Stacpoole (Co-Chair), Ronald Harris-Warrick, Matt Carter, Karen Greif, Bradley Tanner

Panel • Gallatin

Sex Differences in Opioid Use and Outcomes: From Synapses to Circuits

Matthew Hearing (Chair), Anne Murphy, Beverly Reyes, Suman Guha, Eden Anderson (Co-Chair)

Panel • Gibbon

Crossed Wires and Dissolving Priors: State-Dependent Changes in Connectivity Within the Cortico-Thalamic Network

Matthew Banks (Chair), Katrin Preller, Anthony Hudetz, Stefanie Blain-Moraes

Panel • Lake

Stability and Plasticity in Hippocampal and Cortical Networks

Sebastien Royer, Gideon Rothschild, Kamran Diba (Chair), Andrew Maurer

Panel • Lamar

Glutamate Receptors: From Structure to Function

R. Suzanne Zukin (Co-Chair), Sabine Spijker, August Smit, Johannes Hell (Chair)

Panel • Talus

Heterogeneity of Midbrain VTA/SNc Cells and the Properties Underlying Diversity of Neurotransmission

Chris Ford (Chair), Sarah Zych, Vivien Zell, Jorge Miranda-Barrientos, Louis-Eric Trudeau

9:45 A.M. - 11:00 A.M.

Pioneer Session # 2: Eliot Gardner • Amphitheater

More Than 50 Years at WCBR – Brain Reward, Dopamine, the D3 Receptor, Atypical Dopamine Transport Inhibitors, and Cannabinoids

Pioneer: Eliot Gardner
Chair: Amy Newman
Investigators: Andrea Hohmann, Zheng-Xiong Xi

2:00 P.M. - 3:30 P.M.

Career Development Session # 2 • Cheyenne

Tips and Tools for Success in Academia

Lakshmi Devi (Chair), Kyle Frantz, Stephanie Borgland, Lloyd Fricker

3:30 P.M. - 4:30 P.M.

Exhibits & Poster Session III • Jefferson/Madison

4:30 P.M. - 6:30 P.M.

Panel • Amphitheater

The Highs and Lows of GABAergic Transmission in Anxiety: Reconciling Contradictory Findings From Rodents and Humans Studies

Elif Engin, Elizabeth Lucas, Laurence Coutellier (Chair), Georg Oeltzschner

Panel • Canyon

Recent Insights Into the Neurobiological Mechanisms Underlying Opioid Self-Administration and Reinstatement

Marsida Kallupi, Heath Schmidt, Jennifer Fragale, David Reiner (Chair)

Panel • Cheyenne

New Advances in Understanding of Orexin/Hypocretin in Addiction: Converging Evidence From Physiological and Behavioral Models in Multiple Species

Brooke Schmeichel, William Giardino (Co-Chair), Morgan James (Chair), Sarah Leibowitz

Panel • Dunraven/Obsidian

Obesity and the Regulation of Body Weight – It's Not All in Your Head

Carrie Ferrario (Chair), Kevin Williams, Lloyd Fricker (Co-Chair), Darleen Sandoval, Ian Willis

Short Course • Gallatin

New and Evolving Imaging Approaches for Evaluating Neural Circuit Activity

Megha Sehgal, Jonathan Marvin, Vijay Mohan K. Namboodiri, James Otis (Chair)

Panel • Gibbon

Of Shape and Function: Microtubule Remodeling in Neurological and Psychiatric Disorders

Annie Andrieux, Eleanor Coffey, Amynah Pradhan (Co-Chair), Candice Contet (Chair)

Panel • Lake

A Better Pair of Goggles: Super-Resolution Imaging of Synapses

Daniel Choquet, Matthew Dalva, Katharine Smith, Mark Dell'Acqua (Chair)

Panel • Lamar

Why Can't You Hear Me? "Auditory" Circuits in Health and Disease

Patrick Kanold (Chair), Li Zhang (Co-Chair), Merri Rosen, Jan Schnupp, Shaowen Bao, Gregg Recanzone

Panel • Talus

Dopaminergic Modulation of Learning and Cognition

Amy Johnson (Co-Chair), Munir Kutlu (Chair), Daniel Covey, Stephanie Borgland, Joshua Berke

6:30 P.M. - 7:00 P.M.

Refreshment Break • Upper Atrium

7:00 P.M. - 8:30 P.M.

Panel • Amphitheater

Reacting to the Bumps: Diverse Mechanisms Through Which Different Systems Maintain Homeostasis

Shane Hentges (Chair), Zachary Knight, Matt Carter, Stephanie Padilla, Andrew Rau

Panel • Canyon

Computational Models of Inhibitory Control

Alain Dagher (Chair), Michael Frank, Valerie Voon, Frederike Petzschner

Panel • Cheyenne

Candidate Neuroimaging Biomarkers for Synucleinopathies

Xiaoping P. Hu (Co-Chair), Daniel Huddleston (Chair), Kejal Kantarci

Workshop • Dunraven/Obsidian

Life Science Entrepreneurship: Should You Take the Slope That Leads to Commercialization?

Bradley Tanner (Chair), Jason Eriksen, Susan Tappan

Panel • Gallatin

Ventral Striatum Dopamine Encoding of Learning and Motivated Behaviors

Matthew Wanat, Ryan Farero (Chair), Erin Calipari

Panel • Gibbon

Regulation of Motivation for Food, Sex and Drugs by Ovarian Hormones

Tracy Fetterly, Jill Becker, Annabell Segarra, Yanaira Alonso-Caraballo (Chair)

Panel • Lake

Epileptology: From Basic Science to Applied Bioengineering

Olaf Paulson (Chair), Claude Wasterlain, Lars H. Pinborg, Sándor Beniczky

Panel • Lamar

Autism Spectrum Disorder: Mechanisms and Potential Treatments

Brigitta Gundersen (Co-Chair), Hui-Chen Lu, Hsiao-Huei Chen (Chair), Evdokia Anagnostou

WEDNESDAY, JANUARY 29, 2020

6:30 A.M. - 8:30 A.M.

Breakfast at Leisure • Huntley Dining Room/Peaks Restaurant

7:30 A.M. - 9:30 A.M.

Panel • Amphitheater

Synaptic Mechanisms Underlying the Pathophysiology of Autism Spectrum Disorders

Katherine Roche (Chair), Helen Bateup, Anis Contractor, Gavin Rumbaugh

Panel • Canyon

The Point of Snow Return: Long-Term Effects of Adolescent Cannabinoid Exposure on Drug Addiction and Maladaptive Decision Making in Adulthood

Jennifer Wenzel (Chair), Jacqueline-Marie Ferland, Natalie Zlebnik (Co-Chair), Jibran Khokhar, Christie Fowler

Panel • Cheyenne

Transgenerational Inheritance of Stress and Drug Exposure: Effects on Brain, Behavior, and the Epigenome

Lisa Goldberg (Chair), Julie Blendy, Gregg Homanics, Chris Pierce

Panel • Dunraven/Obsidian

Neuroimaging Applications for Social and Affective Modulation of Pain

Vitaly Napadow (Chair), Patrick Finan, Robert Edwards

Panel • Gallatin

The Spectrum of Social Behavior and its Underlying Mechanisms

Marco Venniro (Chair), Marijke Achterberg, Alexa Veenema, Sam Golden

Panel • Gibbon

Inflammation as a Risk Factor for Psychiatric Illness

Victoria Risbrough (Chair), Samantha Friend, Sophie Erhardt, Lilly Schwieler, Margarita Behrens

Panel • Lake

Behavioral Correlates of Circuit and Metabolic Dysfunction in Various Models of Traumatic Brain Injury: Finding Common Ground

Kaitlin Best, Amber Nolan, Akiva Cohen (Chair), Edward Hall

Panel • Lamar

Navigating the Biology of Schizophrenia: From Genetic Risk to Novel Treatment Targets

Brady Maher, Thomas Hyde (Chair), Elizabeth Tunbridge, Robert Sweet

Panel • Talus

Dopamine in Reward and Learning

Briac Halbout, Elizabeth Holly, David Bortz, Kenneth Amaya

10:30 A.M. - 12:00 P.M.

Smitty Stevens Ski Race • Ambush

12:00 P.M. - 2:00 P.M.

Mountain Lunch • Huntley Dining Room

3:30 P.M. - 4:30 P.M.

Exhibits & Poster Session IV • Jefferson/Madison

4:30 P.M. - 6:30 P.M.

Panel • Amphitheater

The Interaction Between Diet and Cognitive Flexibility

Laura Corbit (Chair), Stephanie Borgland (Co-Chair), Amy Reichelt, Alain Dagher

Panel • Canyon

AMPA Receptors in Synaptic Plasticity: From Biogenesis to Potentiation

Ingo Greger, Bernd Fakler, Elva Diaz, Ulli Bayer (Chair)

Panel • Cheyenne

Cells & Circuits Contributing to Opioid Use Disorder

Michael Stefanik (Co-Chair), Giuseppe Giannotti, Emmanuel Darcq, Alexander Smith (Chair)

Panel • Dunraven/Obsidian

Some Will Ski Down the 'Dark Side': Uncovering Neural Substrates of Individual Vulnerability to Mood and Anxiety Disorders

Marek Schwendt (Chair), Lori Knackstedt, Jennifer Rainville, Eric Nunes

Panel • Gallatin

Reward Under a Bad Sign: Neural Mechanisms to Navigate Motivated Action Under Risky Conditions

Catilin Orsini, Michael McDannald, David Jacobs, Michael Saddoris (Chair)

Panel • Gibbon

Sex-Differences in Chronic Pain State From the Bench to the Bedside

Khalid Benamar, Josee Guindon (Chair), Sybil Stacpoole (Co-Chair), Vani Selvan

Panel • Lake

Autism Spectrum Disorder - Bedside to Bench

Angus Wilfong (Chair), Anne Anderson, Heather Born, Richard Frye

Panel • Lamar

There is an Aptamer for That! Nucleic Acid-Based Chemosensors for Brain Research

Tod Kippin (Chair), Kevin Plaxco, Netz Arroyo, Philip Vieira, Karen Scida

Panel • Talus

Adapting to Change: The Circuitry Underlying Behavioral Flexibility

Anna Radke (Co-Chair), David Bortz (Chair), Zackary Cope, Alicia Izquierdo

6:30 P.M. - 7:30 P.M.

WCBR Business Meeting (All are invited and encouraged to attend!) • Gallatin

7:30 P.M. - 9:30 P.M.

Special Poster Session & Reception • Jefferson/Madison

THURSDAY, JANUARY 30, 2020

6:30 A.M. - 8:30 A.M.

Board of Directors Meeting (Invitation Only) • Talus

6:30 A.M. - 8:30 A.M.

Breakfast at Leisure • Huntley Dining Room/Peaks Restaurant

7:30 A.M. - 9:30 A.M.

Panel • Amphitheater

Spatiotemporally-Specific Patterns of Dopamine Release Shape Action Selection

Christopher Howard, Nick Hollon, Anne Collins, Daniel Covey (Chair)

Panel • Canyon

Advances in Cell-Type Specific Detection and Manipulation of Neurotransmitters

David Root (Chair), Jason Dong, Jonathan Marvin, Dillon McGovern, Michael Tadross

Panel • Cheyenne

Neuronal Ensembles and Engrams in Appetitive and Aversive Behaviors

Bruce Hope (Chair), Denise Cai, Leslie Whitaker, Melissa Malvaez, Rajtarun Madangopal

Panel • Dunraven/Obsidian

Après Concussion: Addiction-Related Sequelae of Traumatic Brain Injury

Alana Conti, Christopher Olsen (Chair), Zachary Weil, David Pennington

Panel • Gallatin

Opioid Modulation of Striatal Circuitry Drives Diverse Behavioral Adaptions

William Birdsong (Chair), Sweta Adhikary, Tracy Fetterly, Aya Matsui, Nicolas Massaly

Panel • Gibbon

A Role for Glia in Neuropsychiatric Disorders

Michelle Olsen (Chair), Harry Pantazopoulos, Mikhail Pletnikov, Robert McCullumsmith

Panel • Lake

Schizophrenia: Different Phenotypes / Different Brain Systems

Neil Cashman, George Foussias, Bratislav Misic, Matthias Kirschner (Chair)

Panel • Lamar

A Yardsale of Migraine and Headache Animal Models: New Models and New Developments in Established Ones

Serapio Baca (Chair), Amynah Pradhan, Guido Faas, Michael Morgan, Maggie Waung

3:30 P.M. - 4:30 P.M.

Afternoon Coffee Break • Upper Atrium

4:30 P.M. - 6:30 P.M.

Panel • Amphitheater

Big Sky High: Mechanisms of Endocannabinoid System Control of Brain Function and Nociception

Carl Lupica (Chair), Zsolt Lenkei, Aron Lichtman, Daniel Morgan

Panel • Canyon

Kappa Opioid Receptors: The Multi-Headed Gatekeepers of the Nucleus Accumbens and Motivation

Jessica Barson (Chair), Anushree Karkhanis, Hugo Tejeda, Elena Chartoff

Panel • Cheyenne

DNA Structure and Function – at the Nexus Between Environmental and Genetic Risk for Neuropsychiatric Disorders

Amelia Gallitano (Chair), Cathy Barr, Madabhushi Ram, Robert McCullumsmith

Panel • Dunraven/Obsidian

Sex Differences in Neurodevelopmental Abnormalities Arising From Early Life Insults

Lauren Ellman, Jared Young (Co-Chair), Jennifer Honeycutt, Debra Bangasser (Chair)

Panel • Gallatin

Identifying Neurobiological Substrates of Functional Decline to Help Develop Brain-Interventional Approaches in Normal and Pathological Aging

Mara Mather, Nathan Spreng, Jennifer Bizon, Natalie Ebner (Chair)

Panel • Gibbon

Novel Models for Studying Stress Influence on Alcohol or Substance Use Disorder

Jayme McReynolds (Chair), Jessica Loweth, Daniel Manvich, Jeffrey Tasker

Panel • Lake

Dynamic Neural Encoding of Real-Time Behavioral State Changes in Response to Fear- and Aversion-Inciting Stimuli

Jose Rodriguez-Romaguera, Lindsay Halladay (Chair), Jonathan Fadok, Robert Rozeske

Panel • Lamar

Regulation of Excitability: From Channels to Diseases

Kasper Hansen (Co-Chair), John Gray, Tija Jacob, Terunaga Nakagawa (Chair)

6:45 P.M. - 7:30 P.M.

Cocktail Hour • Huntley Dining Room

7:30 P.M. - 11:00 P.M.

Awards Banquet & Dance • Missouri Ballroom

POSTER SESSION I

SUNDAY, JANUARY 26, 2020 • Jefferson/Madison

S1. Hypothalamic POMC-Expressing Neurons are Activated by Low-Dose Ethanol
Lauren Hood

S2. An Electrochemical Aptamer-Based (E-AB) Biosensor Platform for Real-Time, High Precision Pharmacokinetic and Pharmacodynamic Measurements Within the Brain
Julian Gerson

S3. Perineuronal Net Removal Prior to but Not Following Retrieval Attenuates Cue-Induced Reinstatement in Cocaine Self-Administering Rats
Jereme Wingert

S4. Cocaine-Induced Reinstatement Alters Parvalbumin Cells in the Rat Medial Prefrontal Cortex Following Removal of Perineuronal Nets
Angela Gonzalez

S5. Contributions of Prelimbic-Striatal Circuits to Sex-Based Differences in Risk-Based Choice
Michael Saddoris

S6. KCNQ3 Overexpression Differentially Modulates Cue-Induced Reinstatement of Heroin-Seeking in High- Versus Low-Risk Rats
Britahny Baskin

S7. Open Board

S8. Gut Microbial Compositions Associated With Cocaine Self-Administration in Adult Male Rats
Kyle Frantz

S9. Synthetic Cathinone Mephedrone Causes Chronic Leakage of the Blood Brain Barrier by Downregulation of Membrane-Bound Claudin-5
Tetyana Buzhdygan

S10. Pharmacotherapy Prescribing Patterns in Alcohol Use Disorder (AUD) for Patients Enrolled in the Riahealth Treatment Program (RHTP)
John Mendelson

S11. Decoding Impulsive Decision-Making: Toward Understanding No Friends on Powder Days
Wilder Doucette

S12. The Immediate Response to Trauma in Adulthood Combined With Early Life Stress Predicts Development of Post-Traumatic Stress Disorder
Felicia Gould

S13. Behavioral Adaptations in a Relapsing Mouse Model of Colitis
Chelsea Matisz

S14. Unrestricted Chemogenetic Activation of Norepinephrine Neurons Impairs Attention in the Mouse Continuous Performance Test (rCPT)
Andreas Sørensen

S15. Examining the Mechanisms of Spatial Working Memory Encoding and Retrieval in the Prefrontal-Reuniens-Hippocampal Network
John Stout

S16. Sleep Disturbances in Mice During Chronic THC Administration and Abstinence
Andrew Kesner

S17. Mesoscale Collective Action in the Hippocampus: A Thermodynamic Modeling Approach
Alex Sheremet

S18. Effects of a Natural Anti-Inflammatory Agent in a Model of Alzheimer's Disease
Jason Eriksen

S19. Open Board

S20. IRF8 ASOs Modulate Microglia Responses to an Inflammatory Insult
Fredrik Kamme

S21. Fox DEN: Novel Data Sharing Platform for Sharing Patient Reported Health Information and Genetic Data From the Largest Parkinson's Cohort Worldwide
Luba Smolensky

S22. GABA and Glycine Neurons From the REM Sleep Controlling Ventral Medullary Region Inhibit Hypoglossal Motoneurons: A Mechanism for Obstructive Sleep Apnea
David Mendelowitz

S23. Histological Evidence for Diffusion Rather Than Convective ("Glymphatic") Bulk Flow of Solutes in the Cerebrospinal Fluid (CSF)
Miles Herkenham

S24. Late Perampanel Treatment Stops Midazolam-Refractory Seizures in an Experimental Model of Status Epilepticus
Claude Wasterlain

S25. Distinct Properties of GABA-A Receptors at Synaptic and Extraysnaptic Sites Shape Circuit Patterns During Seizure Evolution
David Naylor

S26. Development of a Novel Locomotor Behavioral Assay to Evaluate the Efficacy of Neurosphere-Mediated Regeneration Following CNS Injury
Taylor Schanel

S27. Induction of Endogenous Reprogramming and Dedifferentiation of Adult Neurons in a Model of Spinal Cord Injury
Jeffery Plunkett

S28. Chronic Glucocorticoid Exposure Primes the Neuroinflammatory Response to Nerve Agent Sarin
Kimberly Kelly

S29. Damage to Thalamic Nucleus Reuniens Following Postnatal Alcohol Exposure Suggests Alterations to Prefrontal-Thalamo-Hippocampal Circuitry
Anna Klintsova

S30. Multiple Circadian Oscillators Mediate Food Anticipation in Rats
Ralph Mistlberger

S31. Effects of Loss of SAP-97 and SAP-102 on Synaptic Plasticity During Motor Learning
Yixuan Pei

S32. AMPA Receptors Intracellular Trafficking; From ER to Plasma Membrane
Françoise Coussen-Choquet

POSTER SESSION II

MONDAY, JANUARY 27, 2020 • Jefferson/Madison

M1. Female Rats Express a More Addictive Phenotype Than Male Rats During Intermittent-Access Heroin Self-Administration
Timothy O'Neal

M2. Exercise Prevents Incubation of Cocaine and Nicotine Craving and Multi-Triggered Relapse to Heroin
Marilyn Carroll

M3. L-DOPA Decrease Oral Fentanyl Consumption
Ryan Farero

M4. Proestrus-Induced Decreases in Heroin Intake in Female Rats
Mark Smith

M5. Prior Cocaine Self-Administration Differentially Alters State Encoding in Distinct Dorsomedial Striatal Neuron Populations in Rats
Lauren Mueller

M6. Ventral Tegmental Area Glutamate Neurons Drive Reinforcement Absent of Dopamine Co-Release
Vivien Zell

M7. Perineuronal Net Degradation Alters Cocaine Reinstatement and Intrinsic Properties of Fast-Spiking Interneurons in the Rat Medial Prefrontal Cortex
Emily Jorgensen

M8. Nucleus Accumbens Cholinergic Interneurons Drive Dopamine Release During Motivated Approach
Joshua Berke

M9. Delineating the Molecular Architecture of the Dopaminergic Presynapse by Super-Resolution Microscopy
Ulrik Gether

M10. Extended-Release Injectable Naltrexone Before vs. After Reentry for Opioid Addicted Prisoners
George Woody

M11. GluA1 Expression in Cortical-Accumbal Circuitry of Differentially Reared Rats
Margaret Gill

M12. Validation of Fos-mRFP Rats to Map Neuronal Ensembles Underlying Reward-Related Behaviors
Katherine Savell

M13. Reward Expectation Differentially Drives Dopaminergic Responses Across Striatal Sub-Regions
Christopher Donahue

M14. Investigating the Role of TrkB in Value-Based Decision Making
Ellen Woon

M15. Prefrontal Neuronal Encoding of Threat-Related Stimuli Across the Estrous Cycle
Marieke Gilmartin

M16. Temporal Dynamics of Spatial Information Encoding Within Retrosplenial Cortex
Megha Sehgal

M17. Making Sense of Computational Psychiatry
Helmut Strey

M18. Neural Precursor Cell Derived Brain-Like Tissue Induces the Formation of Long-Range Connections in the Adult Brain
Gretchen Greene

M19. Sex Differences in Body Composition but Not Neuromuscular Function Following Long-Term, Doxycycline-Induced Reduction in Circulating Levels of Myostatin in Mice
Sonsoles de Lacalle

M20. The Role of Inflammation Markers in Functional Cortical Activation Deficits During Manual Tasks in Postmenopausal Women With Type II Diabetes
Stacey Gorniak

M21. Repeated Mild Traumatic Brain Injury Impairs the Functional Integrity of the Locus Coeruleus-Noradrenergic System
David Devilbiss

M22. Perampanel Treatment of Benzodiazepine-Refractory Status Epilepticus
Claude Wasterlain

M23. Projectile Concussive Impact as a Preclinical Model for Traumatic Brain Injury
Lindsay Michalovicz

M24. CaMKII Versus DAPK1 Binding to GluN2B in Ischemic Neuronal Cell Death After Resuscitation From Cardiac Arrest
Olivia Buonarati

M25. Data Archive for the BRAIN Initiative (DABI)
Dominique Duncan

M26. Characterization of a Novel Allelic Variant of the Human Dopamine D2 Receptor
Kim Neve

M27. A Semi Mechanistic Pharmacokinetic Model to Understand the Metabolic Conversion of Mitragynine to 7-Hydroxymitragynine
Abhisheak Sharma

M28. Can Axons Finding Their Way in Prefrontal Cortex in Neurodevelopmental Disorders?
John Huguenard

M29. Rare Genetic Variants in Monoamine Transports as a Risk Factor for Neuropsychiatric Disease? Insights From a Population Based Case-Control Sample
Freja Herborg

M30. Cocaine Actions on Cortico-Striatal Circuitry: A Focus on Cholinergic Interneurons
Michael Authement

M31. Exploration of Posttranscriptional and Translational Regulation in Depolarized Neuroblasts
Murray Cairns

M32. NRAP-1 is a Protein Ligand for the NMDAR Amino-Terminal Domain
Dayton Goodell

POSTER SESSION III

TUESDAY, JANUARY 28, 2020 • Jefferson/Madison

T1. Hierarchical Cue Control of Cocaine Seeking in the Face of Cost
Anne Collins

T2. In Vivo Identification and Modulation of Appetitive Memory-Related Circuit Elements in the Mouse Prefrontal Cortex
Roger Grant

T3. Investigating the Effects of Controllable Stress on Future Behavioral and Neuronal Responses to Reward- and Drug-Associated Cues
Kayla Siletti

T4. Kappa-Opioid Receptor Antagonism Reverses Heroin Withdrawal-Induced Allodynia
Renata Marchette

T5. Intratelencephalic and Pyramidal Tract Neurons Differentially Mediate Cocaine Sensitization and Conditioned Taste Aversion
Elizabeth Crummy

T6. Neurobiological Correlates of Low Nicotine and Cannabis Exposure
Hugh Garavan

T7. Excitation of Nucleus Accumbens D1 Medium Spiny Neurons and Facilitation of Dopamine Release via Activation of the Muscarinic M1 Receptor Regulates Motivated Behavior
Samantha Yohn

T8. DG3-80: A Novel Fluorescent DAT Ligand Ideal for Live Super-Resolution Microscopy
Amy Newman

T9. Behavioral, Autonomic, and Neural Evidence of Sex Differences in the Human Reward System
Katherine Warthen

T10. Excitatory Regulation From the Parabrachial Nucleus to the Ventral Tegmental Area Mediates Unanticipated Long-Term Memory of Aversion
Smriti Mongia

T11. Genetic Dissection Reveals Different Roles for Intrinsic and Extrinsic Catecholaminergic Innervation of the Cognitive Cerebellum
Erik Carlson

T12. VTA Glutamate Neurons Promote Aversion by Activation of mPFC Parvalbumin Neurons
Huiling Wang

T13. Characterization of the Affective State and Neural Correlates During Empathic Behavior in Rats
Stewart Cox

T14. The Dynamics of Brain Connectivity at Rest Underpins Performance in Task
Yvonne Yau

T15. The Effect of Subthalamic Nucleus Deep Brain Stimulation on Effort Discounting
Guillaume Pagnier

T16. Mechanisms of Prefrontal Circuit Assembly
Benita Jin

T17. Diet Modulates Brain Network Stability, a Biomarker for Brain Aging, in Young Adults
Lilianne Mujica-Parodi

T18. VR Brain Exploration: Explore and Manipulate a 3D Brain to Alter CNS Mechanisms of Satiety and Hunger
Bradley Tanner

T19. Neuronal Protein Tyrosine Phosphatase 1B Drives the Progression of Amyloid β-Associated Alzheimer's Disease
Alex Stewart

T20. Pomalidomide Analogues to Mitigate Neuroinflammation in Neurodegenerative Disorders – From Traumatic Brain Injury to Alzheimer's Disease
Nigel Greig

T21. ITPKB, a Parkinson's Disease GWAS hit, Modulates A-Synuclein Pathophysiology in Cellular Models
Warren Hirst

T22. Characterization of Neural Progenitor/Stem Cell Monolayer and Neurosphere Cultures From Adult Brain Tissue
Raeden Gray

T23. Analysis of Putative Stem and Neural Progenitor Cell Populations Following Traumatic Brain Injury in Adult Zebrafish
Melanie Rojas Hammani

T24. Functional Magnetic Resonance Imaging as an Objective Evaluation of Patients With Cerebral Palsy After Stem Cell Therapy
David Martinez Garza

T25. Expand Your Mind: Evidence for Psychedelic Enhanced Brain Stimulation
Lucas Dwiel

T26. Periaqueductal Gray and Nociceptive Stimulation Activates Ventral Tegmental Area Glutamate Neurons
Leah Pappalardo

T27. MEF2C Hypofunction in Neuronal and Neuroimmune Populations Produces MEF2C Haploinsufficiency Syndrome Behaviors in Mice
Adam Harrington

T28. Risk of Psychosis in Amphetamine and Methylphenidate Treated Youth: Role of Gender
Matej Markota

T29. Time-Delimited Signaling of MET Receptor Tyrosine Kinase Regulates Cortical Circuit Development and Critical Period Plasticity
Shenfeng Qiu

T30. A Structural Basis for How Ligand Binding Site Alterations Can Allosterically Regulate GPCR Signaling and Engender Functional Selectivity
David Sibley

T31. The Effects of NMDA Receptor Partial Agonism on rTMS Motor Plasticity
Joshua Brown

T32. Overexpression of the Neural Chaperone ProSAAS Attenuates the Transsynaptic Spread of Synuclein and Improves Parkinson's Symptoms in Rodent Models of PD
Iris Lindberg

POSTER SESSION IV

WEDNESDAY, JANUARY 29, 2020 • Jefferson/Madison

W1. Heterogeneity in Ventral Striatal Subregion Encoding of Reward Taking and Seeking
Katherine Wright

W2. Defining How Information Encoding in D1 and D2 Medium Spiny Neurons in the Nucleus Accumbens Guides Motivated Behavior
Jennifer Zachry

W3. Chronic Opiate Exposure Alters Mesolimbic Dopamine and Social Behavior
Marc Pisansky

W4. Cocaine Extinction Induces Dendritic Spine Alterations in Projection-Specific Subpopulations in the Rat Infralimbic Cortex
Kelle Nett

W5. Sex Differences in Behavioral Strategies are Accompanied by Altered Neural Circuit Dynamics in Ventral Tegmental Area to Nucleus Accumbens Projections
Amy Johnson

W6. Effect of Lateral Hypothalamus Excitotoxic Lesions on the Acquisition of Sign-Tracking Behavior
Cristina Maria Rios

W7. Investigating the Role of Glucocorticoid Receptor Activation in the Propensity to Attribute Incentive Value to Reward Cues
Sofia Lopez

W8. CRISPR/Cas9 Editing of Neuropeptide Receptor Signaling Reveals an Extended Amygdala Circuit Mechanism Modulating Alcohol Drinking, Anxiety, and Avoidance
William Giardino

W9. Rat Self-Administration of Toluene Vapor
Kevin Braunscheidel

W10. Activation of the Estradiol Receptor, GPER1, Attenuates Preference for Cocaine in Male, but Not in Female Rats
Jacqueline Quigley

W11. Sex Differences in Cholinergic Regulation of Local Nucleus Accumbens Circuit Function Controlling Motivation
Lillian Brady

W12. Beta-Caryophyllene: A Novel Therapeutic Approach for Cocaine Use Disorder
Ewa Galaj

W13. Ethanol Induced Concentration-Dependent Effects on POMC Neuronal Excitability
Jonna Jackson

W14. Modeling Motivation for Alcohol in Humans Using Traditional and Machine Learning Approaches
Erica Grodin

W15. Targeted Epigenetic Editing in the Amygdala Prevents Adulthood Behavioral Pathology Caused by Adolescent Alcohol
John Bohnsack

W16. Cell Type Specific Role of HDAC3 Within the NAc in Regulating Cocaine-Induced Plasticity
Rianne Campbell

W17. Epigenetic Priming Underlies Transcriptional Disruption Linked to Cocaine Relapse
Philipp Mews

W18. Endocannabinoid Signaling in a Septohabenular Circuit Regulates Anxiety-Like Behavior
Casey Vickstrom

W19. Psychostimulants Exert Dose Dependent Effects on Frontostriatal Neuronal Signaling
Robert Spencer

W20. Striatal Melanocortin-4 Receptor Influences Action/Habit Balance in Mice
Elizabeth Heaton

W21. The Role of GIRK Signaling in Prefrontal Cortical Regulation of Affect, Cognition, and Stress Pathology: Implications for Therapeutic Targeting
Eden Anderson

W22. Striatal Dopamine Promotes Cognitive Effort by Amplifying the Benefits Versus the Costs of Cognitive Work
Andrew Westbrook

W23. MRI-Guided Focused Ultrasound and rAAV2-HBKO Lead to Widespread Expression of Transgene in the Brain
Rikke Kofoed

W24. Angiotensin II Signaling Potentiates GABA(A) Receptor Activity of GABAergic Pars Reticulata Projection Neurons
Ratan Singh

W25. Rapid Reprogramming Method Differentiates CuATSM Responders/Nonresponders From ALS Patient Population
Cassandra Dennys-Rivers

W26. Pipsqueak AI: A Standardized and Automated Method of Biomarker Quantification in Digital Histology Using Machine Learning
John Harkness

W27. A Cav2.3-Kv4.2 Complex Regulates A-Type Voltage Gated K+ Currents in Hippocampal Neurons
Jonathan Murphy

W28. Lateral Hypothalamic Fast-Spiking Parvalbumin Neurons Modulate Nociception Through Connections in the Periaqueductal Gray Area
Justin Siemian

W29. Gut–Brain Modulation of Central Thirst Circuitry Controls Satiation
Chris Zimmerman

W30. The Mechanisms and Functional Consequences of Interhemispheric Plasticity
Emily Petrus

W31. LTD Requires Engagement of Two Distinct Mechanisms for Suppression of CaMKII Synaptic Targeting
Sarah Cook

W32. Biased Modulation of a Ligand-Gated Ion Channel
Riley Perszyk

Panel Session Abstracts

SUNDAY, JANUARY 26, 2020

Opening Plenary

PLENARY • SUNDAY • 8:30 A.M. - 9:30 A.M. • MISSOURI BALLROOM

How the Stroke Stopwatch was Shattered

Presenter: Gregory Albers

The last few years have seen unprecedented progress in the treatment of acute stroke. Major advances include the 2015 endovascular trials that established a 6-hour treatment window for endovascular therapy followed by the 2018 studies that expanded the treatment window to 24 hours using advanced imaging. In addition, 2 studies have demonstrated that the window for intravenous thrombolysis can be extended using advanced imaging.
The underlying theme of these advances is that every stroke evolves in a unique manner and that imaging techniques now allow identification of patients with salvageable tissue. Selecting patients with salvageable tissue for enrollment in stroke studies can lead to robust treatment effects with a limited sample size. These advances now open the door to a re-evaluation of neuroprotective therapies as well as testing even longer time windows for reperfusion therapies. Recent studies indicate that the assessment of collaterals using perfusion imaging can accurately predict the speed of infarct core growth in the early hours after symptom onset. Therefore, patients who are most likely to have early growth can be targeted for neuroprotective therapies.
In this lecture, we will review the design and results of the most influential recent acute stroke studies as well as the changes in stroke guidelines that occurred as a result of these trials. We will also examine the role of advanced imaging with automated software programs that allow rapid and accurate determination of the volume and location of salvageable tissue.

Pioneer Session # 1

PIONEER SESSION • SUNDAY • 9:45 A.M. – 11:00 A.M. • AMPHITHEATER

Understanding the Neurobiological Basis of Depression

Pioneer: Fritz Henn
Chair: Lloyd Fricker
Investigators: Bo Li, Alexander Sartorius

The presentations at WCBR began in the late 70's with studies of GABA and GLU uptake which suggested that asrocytes played a significant role in controlling synaptic concentrations of GLU and GABA which was contrary to the accepted view at the time that presynatic uptake regulated the level of synaptic transmitter. This led to the idea of the tripartate synapse. Subsequently we began to focus on depression and worked with an animal model developed by Seligman, learned helplessness. Our contribution to this model was the development of lines of animals either showing helplessness without training or becoming resistant to the development of helplessness. Using these lines, we mapped the circuits mediating helpless behavior and showed that inputs from the HPA axis, hippocampus and amygdala as well as PFC converged in the l. habenula, a small nucleus lying near the thalamus. There these signals were integrated and processed and the output from the habenula controlled the aminergic nuclei, regulating the release of NE, DA and 5HT. This appeared to us to be a central pathway controlling depressive behavior and thus we suggested that this pathway could result in relieve depression. To test this idea, we suggested that intractable depression might be relieved by deep brain stimulation of the l. habenula. In animal experiments we showed this to be the case and that CAM kinase in the l. habenula appeared central to the control of mood. This was tested in treatment resistant depression using deep brain stimulation in the l. habenula and proved to be effective. The final work prior to my retirement was presented at WCBR and involved showing that CAM kinase in the l. habenula was central to maintaining a normal mood and that when it was deleted just in that structure helpless behavior resulted, when it was replaced normal affect resulted.

PANEL • SUNDAY • 12:30 P.M. - 2:00 P.M. • DUNRAVEN/OBSIDIAN

Conan Kornetsky's Memorial Panel

Chair: Jacqueline McGinty
Presenters: George Koob, Linda Porrino, Chris Pierce, David Root

The scientific community lost a towering pioneer in addiction research on December 21, 2018. Conan Kornetsky, D. Phil. was an active faculty member and researcher in the Departments of Psychiatry and Pharmacology at Boston University Medical School where he remained from the mid-1960s until his retirement. Dr. Kornetsky (Conan) had a great and never diminishing love of science. He was a great mentor to young people and he loved to ski. He received several awards celebrating his mentorship and distinguished research record. He was an active participant in WCBR annually for over 40 years. His research was focused on determining the neuronal mechanisms involved in the hedonic effects of drugs of abuse and the ways in which environmental cues influence long-term drug effects. This panel will present fond memories of Conan's friendship and the famous Conan Kornetsky Ski Club at WCBR as well as some of the pioneering research that he performed and collaborated in over the years. Jakie McGinty will introduce the audience to Conan and his love of WCBR. George Koob will recount his close friendship with Conan beginning in the early 1980's when they fast became friends at WCBR. He will recount some of the many seminal contributions Conan made. Early on he used human laboratory studies to identify attentional deficits in subjects with schizophrenia laying the foundation for some of the modern attentional theories of the disease. He then moved on to develop an animal model for measuring thresholds for brain stimulation reward that eliminated response artefacts (rate free brain stimulation reward threshold procedure). He followed this work by showing that all drugs of abuse produce lower thresholds for brain stimulation reward. Together this body of work opened the door for not only the study of the neuropharmacology of drug reward but also the neuropharmacology of loss of reward in addiction. Linda Porrino, a close collaborator, will discuss Conan's pioneering role in developing intracranial self-stimulation methods as a means to determine pharmacological effects on brain reward and aversion systems. She will describe recent work that continues to use these approaches to evaluate the effects of opioids and nicotine. Chris Pierce, a former colleague at BU, will discuss experiments examining the mechanisms of action of deep brain stimulation in the context of its ability to attenuate the reinstatement of cocaine seeking. This line of experimentation originated in collaboration with Conan as we modified his self-stimulation equipment to administer the deep brain stimulation. Conan's contributions to WCBR were significant and those who knew him will long remember his intellectual generosity and friendship. David

Root, the inaugural Conan Kornetsky Travel Fellow, will present phototagged electrical recordings data and glutamate and GABA dynamics that underlie the changes in firing during motivated behavior.

Career Development Session # 1

SPECIAL SESSION • SUNDAY • 2:00 P.M. – 3:30 P.M. • CHEYENNE

NIH Grant Application & Reviews

Chair: Brad Cooke
Participants: David Devilbiss, Lakshmi Devi, Gretchen Snyder, Paul Phillips, Dana Plude

Attendees of this session will be provided information about the lifecycle of an NIH grant, from brilliant idea to peer review in a study section to the release of funding and tips on how, when, and whom to interact with at the NIH. The session will conclude with a 'mock' study section that will show what happens in a study section, and convey a few key points that can spell the difference between a successful and unsuccessful grant application.

Sunday Afternoon Panel Sessions

PANEL • SUNDAY • 4:30 P.M. - 6:30 P.M. • AMPHITHEATER

Contribution of Glia to Brain Function and Disorders

Chairs: Hye Young Lee, Martin Paukert
Presenters: Yongjie Yang, Martin Paukert, Long-Jun Wu, Hye Young Lee

Glia play active and diverse roles in modulating neuronal/synaptic functions in the CNS. This panel will discuss recent findings on novel mechanisms of glia, particularly astrocytes and microglia, in normal and pathological brain function. In the first part of the session, we will focus on the role of astrocytes. Yongjie Yang will introduce a new finding on how astrocytes are regulated by neurons through secreted neuronal exosomes. He will further discuss the neuron-specific miR-124 in secreted exosomes in brain disease models, including amyotrophic lateral sclerosis (ALS), and how astroglial exosomes modulate neuronal functions. Martin Paukert will present mechanisms of behavioral state-dependent cortical astrocyte Ca2+ dynamics. Combining timed locomotion paradigms with pharmacological and genetic manipulations, he revealed that α1a-noradrenergic signaling is responsible for locomotion-induced astrocyte Ca2+ elevations, and that cholinergic signaling takes a facilitating role. Thus, neuromodulators interact to appropriately inform astrocytes about the behavioral state. In the second part of the panel, we will discuss about the role of microglia. Long-Jun Wu will demonstrate that microglia in awake mice

have relatively reduced process surveillance compared with those under general anesthesia. He will further discuss that noradrenergic tone in awake mice normally suppresses microglial process surveillance, indicating the importance of awake imaging for studying microglia-neuron interactions and advancing a "set point" theory for how neuronal activity influences microglial process dynamics. Lastly, Hye Young Lee will focus on the contribution of microglia in the pathological condition of fragile X syndrome (FXS), the most common monogenic cause of autism spectrum disorders. She will demonstrate an exaggerated response of microglia to neuroinflammation in the mouse model of FXS and how microglia contribute to the pathophysiology of FXS.

PANEL • SUNDAY • 4:30 P.M. - 6:30 P.M. • CANYON

Neuroendocrine and Neuroimmune Modulation in Stress and Addiction

Chairs: Carolina Haass-Koffler, Dean Kirson
Presenters: Dean Kirson, Zoe McElligott, Kelly Cosgrove, Carolina Haass-Koffler

Increasing evidence supports the role of the neuroendocrine and neuroimmune systems in the development of stress and addictive disorders. The stress system has a well-established role in the addiction process by promoting dependence-associated escalation of alcohol drinking and other addictive substances; however, the underlying signaling mechanisms and circuitry remain unclear, which limits therapeutic utility. This panel will provide translational perspectives on the role of neuroendocrine and neuroimmune modulation in the context of stress and addiction by highlighting novel molecular mechanisms and new neural pathways connecting these systems. Dr. Dean Kirson (Scripps Research Institute) will show how the anti-stress neuropeptide oxytocin opposes the alcohol-induced elevation in stress-related GABA neurotransmission in the amygdala. Dr. Zoe McElligott (University of North Carolina) will present the role of noradrenergic signaling in stress susceptibility and resilience. Dr. Kelly Cosgrove (Yale University) will show the dynamic neuroimmune response to lipopolysaccharide (endotoxin) using a novel paradigm of positron emission tomography radiotracing of the immune sensitive protein TSPO, and how this neuroimmune response is suppressed in individuals with addiction (tobacco smokers) and stress disorders (PTSD). Finally, Dr. Carolina Haass-Koffler (Brown University) will present evidence on the variation of neuropeptides including beta-endorphin, oxytocin, substance P and orexin and the effect of appetite hormones on glucocorticoids and mineralocorticoids in individuals with alcohol use disorder (AUD). Dr. Haass-Koffler (Brown University) will lead discussion of the presentations, emphasizing the translational efforts and recent advances in our understanding of the interplay between neuroendocrine and neuroimmune modulation in stress and addiction.

PANEL • SUNDAY • 4:30 P.M. - 6:30 P.M. • CHEYENNE

Kratom –Potential Drug of Abuse or Useful Analgesic Without Opioid-Like Side-Effects?

Chairs: Daniel Morgan, Jenny Wilkerson
Presenters: Christopher McCurdy, Abhisheak Sharma, Lance McMahon, Jenny Wilkerson

Although touted as a "legal high" by some, there are innumerable anecdotal reports of kratom use to control chronic pain, opioid addiction, and opioid withdrawal with a limited liability profile. In February 2018, the United States (US) Food and Drug Administration warned there was no evidence that kratom was safe or effective for any medical use and likened its chemical compounds to opioids. This symposium will seek to fill the knowledge gap surrounding kratom, bringing together expert scientists to review the current knowledge of the chemistry, pharmacology, behavioral side effects, and therapeutic potential of kratom and at least two of its alkaloid components, mitragynine and 7-hydroxymitragynine. Dr. Morgan will introduce the symposium. Dr. McCurdy will review the history and chemistry of the tree that kratom is derived from, Mitragyna speciosa. Dr. Sharma will detail what is known about the pharmacokinetics and alkaloid composition of the natural product found in Malaysia and currently available US commercial formulations. Dr. McMahon will present the findings from recent rodent behavioral neuropharmacology studies examining the reinforcing, abuse-related, and physiological effects of kratom, mitragynine, and 7-hydroxymitragynine. Finally, Dr. Wilkerson will present recent findings from rodent behavioral neuropharmacology studies examining the effects of kratom and key alkaloid components for the treatment of neuropathic pain. Upon the conclusion of these presentations, a discussion session will evaluate both benefits and detriments attributed to this controversial natural product, with an attempt to forge consensus on future directions of research, emphasizing key points related to the pharmacology of kratom. This work to better understand the complex neuropharmacology of kratom and its alkaloids will facilitate the development of enduring chronic pain and opioid use disorder therapeutics with a lessened abuse and untoward physiological side-effect profile.

PANEL • SUNDAY • 4:30 P.M. - 6:30 P.M. • DUNRAVEN/OBSIDIAN

Frontal Cortical Regulation of Motivated Behaviors

Chairs: Vijay Mohan K. Namboodiri, Cody Siciliano
Presenters: Evan Hart, Cody Siciliano, Christina Gremel, Vijay Mohan K. Namboodiri

Understanding the neuronal mechanisms mediating motivated behaviors is a major goal of neuroscience. While such behaviors are orchestrated by the coordinated activity of multiple brain regions, the prefrontal cortex is a central node governing such behaviors. This panel will introduce a broad audience to recent advances in our understanding of rodent frontal cortical circuit function. Dr. Hart will present data on the role of the rat anterior cingulate cortex (ACC) in mediating the discrimination of options during effort-based decision-making. Using calcium imaging and chemogenetics, these data will highlight how activity in ACC during effort-based decision-making reflects task-specific conditions for choice, and the effect of activation or inhibition of ACC on choice-specific behavioral execution. Dr. Siciliano will discuss how the activity of neurons measured using single-cell calcium imaging approaches in the mouse medial prefrontal cortex encode stimuli with positive and negative valence. He will then highlight how dysregulation of this process can contribute to the development of compulsive behaviors. Dr. Gremel will present data showing the circuit mechanisms underlying lateral orbitofrontal cortex computations supporting goal-directed decision-making in mice. Using in vivo calcium imaging and activity manipulations during behavior, combined with ex vivo whole cell physiology, she will show a thalamic driven disynaptic circuit that supports the updating of goal-directed decision-making. Dr. Namboodiri will present two-photon calcium imaging data showing rapid timescale plasticity in reward responses within the mouse ventromedial orbitofrontal cortex. These data will show that select neuronal subpopulations within this region convey reward responses as a relative comparison between a received reward and short-term memory of previously experienced motivational stimuli. He will then discuss how these results support our understanding of reward learning.

PANEL • SUNDAY • 4:30 P.M. - 6:30 P.M. • GALLATIN

Neural Systems Mediating Passive and Active Responses During Aversive Situations

Chair: Matthew Wanat
Presenters: Lindsay Halladay, Mahsa Moaddab, Maria Diehl, Matthew Wanat

Survival in one's environment depends upon learning and responding appropriately during aversive situations. These behaviors can include both defensive reactions as well as active responses to avoid the aversive outcome. The behavioral response toward aversive stimuli is not governed by a single

brain region, but rather arises from a complex interplay between cortical, amygdala, hippocampal, midbrain, and striatal circuits. This panel will highlight recent research that employs electrophysiological recordings, voltammetry recordings, chemogenetics and optogenetics to elucidate the various neural systems that contribute to fear conditioning and active avoidance. Lindsay Halladay (Santa Clara University) will discuss how the projections from the infralimbic cortex to the bed nucleus of the stria terminalis enables adaptive responding when aversive cues are ambiguous. Mahsa Moaddab (Boston College) will present findings on the neuronal activity within the retrorubral field during the discrimination of danger, uncertainty and safety. Maria Diehl (Kansas State) will discuss how the projections between the prelimbic cortex, basolateral amygdala, and ventral striatum control active avoidance. Matt Wanat (UTSA) will discuss how distinct patterns of dopamine signaling within the ventral medial and ventral lateral striatum are predictive of active avoidance learning. Together, this panel will highlight the diverse neural systems that are involved with the behavioral responding toward aversive events.

PANEL • SUNDAY • 4:30 P.M. - 6:30 P.M. • GIBBON

New Treatment Strategies for Mood Disorders: From IBT to ECT

Chair: Anil Malhotra

Presenters: Anna Van Meter, Anil Malhotra, Daphne Voineskos, Miklos Argyelan

The treatment of mood disorders encompasses multiple therapeutic strategies including psychotherapeutic, pharmacological and neuromodulatory approaches. In this panel, we will present data across a range of treatment modalities to provide an overview of developing work in this area. Anil Malhotra (Hofstra/Northwell) will chair the session and provide introductory remarks about treatment of mood disorders. Anna Van Meter (Hofstra/Northwell) will present results from a randomized clinical trial of interpretation bias training (IBT), a computer-based intervention designed to alter negative emotion processing bias to improve social functioning and mood. Young adults with bipolar disorder (N=50) randomized to IBT (versus a sham intervention) shifted their emotion interpretation to see faces as happy, rather than sad, and experienced reduced symptoms of depression. Anil Malhotra (Hofstra/Northwell) will next discuss the use of novel pharmacological agents to treat cognitive dysfunction in bipolar disorder. Data from clinical trials with the stimulant modafinil and the dopaminergic agonist pramipexole, demonstrated cognitive-enhancing effects. The safety profiles, which included the risk of converting a stable patient into mania, was also favorable. Next, Daphne Voineskos (Univ of Toronto) will discuss transcranial magnetic stimulation (TMS), including data from a novel TMS variant, intermittent theta burst stimulation, to treat major depression. Finally, Miklos Argyelan (Hofstra/

Northwell) will conclude the session with new data on electroconvulsive therapy (ECT). His electrical field (E-field) modeling work (n=150) revealed a robust relationship between ECT induced E-field strength and neuroanatomical changes that occurred during treatment. These data suggest that E-field guided ECT may be useful to minimize cognitive side effects. Taken together, we hope that this panel will provide a new perspective on the breadth of new treatment approaches in mood disorders.

PANEL • SUNDAY • 4:30 P.M. - 6:30 P.M. • LAKE

Synaptic Transmission and Plasticity Regulated by Neurotransmitter Receptor Auxiliary Subunits

Chair: David Bredt

Presenters: Yael Stern-Bach, Andres Maricq, David Bredt, Wei Lu

Molecular cloning initially determined that neurotransmitter-gated ion channels comprise multimeric subunits, which contain both the ligand binding and the ion channel functionalities. Subsequent studies identified auxiliary subunits that regulate certain neurotransmitter receptor channels. This panel will describe the physiological roles such auxiliary subunits play in controlling four classes of synaptic ligand-gated ion channels.

The first presentation concerns AMPA receptors, the primary mediators of fast excitatory synaptic transmission. Stern-Bach will discuss how members of two auxiliary protein families, TARP and Shisa/CKAMP, independently and combinatorially, modulate AMPA receptor function. Maricq will discuss findings from genetic studies that provide new mechanistic insights into the function of NMDA receptors, which control activity-dependent changes in synaptic plasticity. Maricq's studies identify NRAP-1, a LDLa domain protein released by presynaptic neurons that determines synaptic strength by modulating NMDAR gating. Nicotinic acetylcholine (nACh) receptors mediate synaptic transmission, control neurotransmitter release and mediate nicotine addiction. Bredt will present genome-wide expression cloning studies that identify accessory components for several nACh receptor subtypes. He will describe both nACh receptor chaperones and auxiliary subunits. GABAA receptors mediate synaptic inhibition to control neural circuit information processing and GABAA receptors are targets for numerous medicines. Whether GABAA receptors contain auxiliary subunits that regulate trafficking, kinetics and pharmacology has remained unknown. Lu will discuss an auxiliary subunit of GABAA receptors that is critical for controlling these aspects of GABAA function. Taken together this panel elaborates a general role for ion channel accessory proteins in regulation of AMPA, NMDA, nACh and GABA receptors and provides new insights in neurophysiology and neuropharmacology.

PANEL • SUNDAY • 4:30 P.M. - 6:30 P.M. • LAMAR

New Approaches to Treating Patients in Status Epilepticus

Chair: Denson Fujikawa
Presenters: Thomas Bleck, Hilary McCarren, Claude Wasterlain, Denson Fujikawa

The approach to treating patients with status epilepticus (SE) in general, and refractory SE (RSE) in particular, has always been to eliminate electrographic seizure discharges (ESDs). In the case of RSE, this has been at the expense of brain health, since the longer that SE lasts, the greater and more widespread the neuronal necrosis, morbidity and mortality. Animal studies for the past 25 years have shown remarkable neuroprotection with NMDA-receptor antagonists, including ketamine, in chemically or electrically induced clonic SE in rodents, even with persistent ESDs, yet neuroprotection has never been considered in human SE. A new antiepileptic drug (AED) to stop SE has not been proposed in years. In addition, giving several AEDs at the onset of SE instead of the stepwise approach of giving one at a time has not been considered in order to prevent RCSE. Thomas Bleck will discuss the current approach to treating SE. Hilary McCarren will discuss the use of the $\alpha 2$ adrenoceptor agonist dexmedetomidine in stopping midazolam-resistant ESDs and protecting neurons following injection of the organophosphate nerve agent soman. Claude Wasterlain will present evidence that starting treatment with several AEDs with complementary mechanisms of action is more effective than a stepwise approach in stopping SE. Finally, Denson Fujikawa will present evidence that early use of ketamine for neuroprotection in SE, shown to be remarkably effective in the rodent, can guide a prospective clinical trial in human SE. A biomarker for neuronal damage in the human and the rat, serum neuron-specific enolase, could also serve as a biomarker for neuroprotection by ketamine in human clinical trials.

Sunday Evening Panel Sessions

PANEL • SUNDAY • 7:00 P.M. - 8:30 P.M. • AMPHITHEATER

Pain and Itch: How are They Motivating You?

Chair: Paul Phillips
Presenters: Tamara Markovic, Amber Alhadeff, Tayler Sheahan

There is strong recognition that somatosensory processes can interact with motivated behavior in ways that can have major impact on quality of life (e.g., workdays lost to chronic pain, increased risk of substance use). However, attempts to understand the neural mechanisms linking these processes is still a nascent field of research. The somatosensory perceptions of pain and pruritus (itch) have often been considered to be different grades of a singular process.

However, as more is learned about the neural substrates underlying these processes, it has become evident that they are mechanistically separable. Very recently, evidence has emerged that circuits mediating pruritus, like those mediating pain, interact with neural substrates of motivated behavior. This panel will provide discussion around these points. First, Tamara Markovic (Washington University) will describe the effects of pain on the activity of dopamine neurons in the ventral tegmental area and how these effects drive pain-induced anhedonia and loss of motivation for goal directed behaviors. Next, Amber Alhadeff (University of Pennsylvania) will discuss the effects of hunger on pain. She will describe how a subpopulation of hypothalamic neurons expressing agouti-related protein (AgRP) selectively inhibit inflammatory pain. Tayler Sheahan (University of Pittsburgh) will then introduce circuitry that mediated pruritus. She will show, from studies mapping spinal neurons that express the neurokinin-1 receptor, that a subset of these neurons projects to brain regions where pain interacts with motivated behavior.

PANEL • SUNDAY • 7:00 P.M. - 8:30 P.M. • CANYON

Viral Vectors for Gene Modifications to Enable Axon Regeneration

Chair: Oswald Steward
Presenters: Kevin Park, Binhai Zheng, Oswald Steward

There is a pressing need to identify interventions that can enable regenerative growth of CNS neurons after injury. Studies over the past decade have identified genes that can be targeted to enhance regeneration and recent advances in viral vector technologies are providing powerful platforms to introduce genetic modifications in adult neurons in vivo. Challenges remain, however, because of the molecular heterogeneity of CNS neuron types and the unique neurotrophic properties of different viral vectors. This panel will discuss examples of the use of AAV vector technologies to introduce genetic modifications in different populations of CNS neurons. Kevin Park will describe approaches using viral vectors that target different types of neurons in the visual system and how they could be harnessed as a therapeutic intervention to regenerate a damaged visual pathway. Binhai Zheng will discuss results from using viral vectors in conjunction with genetically modified mice to assess the role of neuron intrinsic and extrinsic factors in the multicellular response to spinal cord injury. Such studies provide important in vivo evidence on molecular pathways in axon regeneration, sprouting and astrocyte response. Oswald Steward will discuss recent results using novel technologies involving retrogradely-transported AAVs to deliver gene modifying cargoes to cells of origin of multiple spinal pathways interrupted by spinal cord injury. The final part of the session will be a didactic

panel discussion on principals of AAV biology that impact on development of effective gene modifying vectors and considerations for the potential translation of AAV-based technologies to human therapeutics.

PANEL • SUNDAY • 7:00 P.M. - 8:30 P.M. • CHEYENNE

It's Not All Dopamine: The Role of Serotonin in the Regulation of Impulsive Behavior

Chair: Katherine Nautiyal
Presenters: Catharine Winstanley, Noelle Anastasio, Katherine Nautiyal

While dopamine is generally regarded as the major modulator of impulsivity and risky decision making, a large body of evidence now shows that serotonin has an important role in regulating these behaviors. The multi-dimensional aspects of these behavioral systems coupled with the complexities of serotonin signaling make this topic timely especially as new behavioral and neuroscience measures emerge. The goal of this symposium is to discuss the scope and mechanisms of serotonin control over these behavioral and cognitive systems. Dr. Winstanley will focus on the extent to which serotonin plays a role in decision making in the cognitive effort task. Dr. Anastasio will discuss cortiocostriatal neurocircuitry and its regulation by 5-HT2R systems in substance use disorder behaviors, with a series of findings that collectively indicate that the inhibition of the 5-HT2AR and/or the activation of the 5-HT2CR improve impulsivity, with collateral diminution of drug-seeking behavior. Dr. Nautiyal will present data which help clarify the neural circuit mechanisms of how serotonin interacts with reward systems via 5-HT1BR signaling to influence impulsivity. Overall, the speakers will highlight advances in our understanding of the mechanisms of serotonin control of impulsive behavior, and the panel will discuss the implications of these findings.

PANEL • SUNDAY • 7:00 P.M. - 8:30 P.M. • DUNRAVEN/OBSIDIAN

Long-Term Behavioral and Neurobiological Effects of Adolescent Drug Use

Chair: Elizabeth Pitts
Presenters: Elizabeth Pitts, Anushree Karkhanis, Mary Torregrossa

Adolescence is a developmental period characterized by increased risk-taking, impulsivity, and vulnerability to developing substance use disorders. Additionally, emerging evidence indicates that substance use during adolescence confers increased vulnerability across the lifespan, altering decision making and increasing risk and severity of substance and alcohol use disorders in adulthood. It is imperative to understand the long-term behavioral changes following adolescent drug use, and the lasting neurobiological mechanisms

mediating these behavioral alterations, that may underlie life-long increases in vulnerability. Our panel will present data on long-term behavioral and neurobiological changes in rodent models observed following adolescent exposure to 3 different drugs of abuse. We will examine commonalities and differences in various behavioral models following exposure to a variety of drugs of abuse during adolescence and corresponding changes in mesolimbic circuitry. Dr. Pitts will speak about how adolescent, but not adult, self-administration of nicotine increases anxiety-like behaviors and alcohol consumption in adulthood and alters nAChR modulation of dopamine in the NAc. Dr. Karkhanis will then speak about changes in adult social interaction and dopamine release in the NAc following ethanol exposure in early and late adolescence. Finally, Dr. Torregrossa will close the session by discussing how Tetrahydrocannabinol (THC) self-administration in adolescence alters adult working memory. Together, this panel will highlight the unique and lasting impact that drug exposure during adolescence can have on behaviors and neurobiology and explore the role these changes may play in increasing lifetime vulnerability to substance use disorders.

PANEL • SUNDAY • 7:00 P.M. - 8:30 P.M. • GALLATIN

Cholinergic Modulation Shapes Striatal Microcircuitry: Roles in Reinforcement Learning and Reward-Seeking Behavior

Chair: Samantha Yohn
Presenters: David Lovinger, Kate Wassum, Samantha Yohn, Mark Ferris

Nucleus accumbens (NAc) dopamine (DA) is an important component of brain circuitry regulating motivated behavior and reward processing. Cholinergic transmission and cholinergic tone is a critical regulator of midbrain DA neuron activity, NAc DA release, and guides reward-related behavior. Acetycholine (ACh) exerts its actions through activation of muscarinic (mAChR) and nicotinic (nAChR) receptors. Within the NAc, cholinergic interneurons (CINs) can initiate DA release through activation of nAChRs on DA terminals and fine-tune output of medium spiny neurons (MSNs). Together, these findings highlight the modulatory role of ACh on NAc microcircuitry and behavior, and further suggest that therapeutics targeting the cholinergic system may be beneficial in attenuating reward-related deficits observed across several disorders. This panel aims to focus on recently developed methods for monitoring ACh, novel therapeutics to delineate the role of individual NAc mACh subtypes, and genetic tools to characterize cholinergic signaling. Dr. David Lovinger will first present novel data on the utility of the intensity-based ACh sensing fluorescent reporter (iAChSnFR) bio-sensor to probe the function of ACh dynamics in response to drugs of abuse, and the acquisition of a Pavlovian conditioning task. Next, Dr. Kate

Wassum will discuss how NAc ACh regulates DA release to gate the availability of reward predictive cues. Dr. Samantha Yohn will then highlight the role of the M1 and M4 receptors in motivated behavior through use of positive allosteric modulators (PAMs). Finally, Dr. Mark Ferris will present data focused on individual differences in ACh release as a predictor of motivated behavior. Collectively, the panel provides innovative findings on the regulatory role of ACh and its receptors on NAc DA release and DA-dependent behaviors, which may have implications for understanding the neurocircuitry underlying maladaptive motivation and foster the development of novel therapeutics.

PANEL • SUNDAY • 7:00 P.M. - 8:30 P.M. • GIBBON

Investigating Brain Circuits in Neurodevelopmental Disability, From Molecular to Electrophysiological Aspects

Chair: Francois Bolduc
Presenters: Francois Bolduc, Sarah Lippe, Jean-Francois Lepage

Neurodevelopmental disability (NDD) affects 13% of the population and include a wide range of diagnosis from ADHD and learning disability to intellectual disability and autism spectrum disorder. NDD is increasingly recognized to be related to genetic etiologies. Nonetheless, the role of specific genes in relation to specific brain regions remains unknown in most cases in human, and often not taken into account in designing trials. We postulate that designing interventions aiming at behaviors modification (pharmacological or not) should include an understing of the spatio-temporal expression of the gene (s) targeted by the intervention.

Our panel is composed of leaders in the molecular genetics and electrophysiological investigation of Neurodevelopmental disabilities. Francois Bolduc (University of Alberta) will present evidence for variation in molecular expression as well as novel methods aimed at gaining a deeper understanding of the molecular clustering in relation to brain location and temporal profile using machine learning. He will include both human and animal model data. Sarah Lippe (Universite de Montreal) will present findings obtained using electroencephalography (EEG) in context of learning and memory formation in individuals with NDD which reveal surprising characteristics of brain circuits in NDD. Jean-Francois Lepage (Sherbrooke University) will present data from individuals with NDD at baseline and in clinical trial obtained with EEG and transcranial magnetic stimulation (TMS) able to correlate neuronal activity with molecular processes including neurotransmission.

Our multidisciplinary panel will discuss how integration of molecular and electrophysiological data with a focus on task-to-brain circuit could shed light on cognition but also provide a better understanding of the response to treatment in clinical trial. We will propose a new framework for the design of trials and assessment of clinical response.

PANEL • SUNDAY • 7:00 P.M. - 8:30 P.M. • LAKE

Obesity Induced Changes to Brain Motivation Circuits

Chair: Richard O'Connor
Presenters: Richard O'Connor, Bridget Matikainen-Ankney, Morgan James

Obesity and poor dietary habits rank as a leading cause of preventable of death in American adults second only to tobacco use. Obesity is characterized by a dysregulation of a host of motivated behaviors, including feeding and activity patterns that ultimately lead to caloric intake that far supersedes energy demands. Over the past decade technological advancement in neuroscience research tools has led to a rapid expansion of our understanding of the neuronal motivational circuitry controlling feeding and energy expenditure. However, how obesity reshapes communication within these neuronal networks has not kept pace, though human and rodent behavioral data suggest obesity imparts lasting effects on aspects of these circuits. Such persistent changes may contribute to further weight gain, ultimately establishing obesity as a chronic disorder. Targeting such corrupted motivational signaling may serve as a viable therapeutic strategy for reversing the hyperphagia and motivational deficits associated with obesity correcting caloric intake to match energy expenditure. This panel will present unpublished emerging research characterizing obesity induced changes to the brain's motivational circuitry and the contribution of such changes to the development of a range of behavioral deficits. Dr. Richard O'Connor (Icahn School of Medicine at Mount Sinai) will present work highlighting habenular control of obesity-related abnormalities in food preference and motivation. Dr. Bridget Matikainen-Ankney (Washington University School of Medicine) will discuss work outlining the effects of weight loss after obesity on physical activity, food motivation, and underlying accumbal circuits. Dr. Morgan James (Rutgers University) will present work demonstrating that plasticity in the orexin-midbrain dopamine circuit underlies enhanced motivation for palatable food in obese female rats with a history of binge-like eating.

PANEL • SUNDAY • 7:00 P.M. - 8:30 P.M. • LAMAR

Visual Circuit Function and Plasticity

Chair: Huizhong Tao
Presenters: Jianhua Cang, Nicholas Priebe, Sandra Kuhlman, Hey-Kyoung Lee

Neural circuits in the mammalian visual system carry out complex tasks including the reception of light and formation of monocular representations, buildup of a binocular perception and guiding body movements in relation to objects seen. The visual circuits can be highly sensitive to changes of sensory experience during development as well as in adulthood. Understanding how neurons interact within a local circuit and through long-range projections

and how they change connectivity in adaptation to dynamic environments is essential for comprehending how the tasks are achieved. These issues are being addressed with enriched imaging, electrophysiology, optogenetics and behavioral approaches. In this panel, Dr. Jianhua Cang (UVA) will present recent results regarding the visual transformations that take place in the retinocollicular pathway, especially for the processing of motion direction. Dr. Nicholas Priebe (UT) will discuss the computations performed by visual cortex that integrate binocular information and generate a representation of the world in three dimensions. Dr. Huizhong Tao (USC) will describe recent findings of how information processing in primary visual cortex is shaped by visual input conveyed by a higher-order thalamic nucleus pulvinar. Dr. Sandra Kuhlman (CMU) will discuss adaptive plasticity mechanisms that improve natural scene encoding in primary visual cortex and application of this knowledge to rescue function in animals deprived of early visual experience. And Dr. Hey-Kyoung Lee (JHU) will report input-specific homeostatic synaptic adaptation to changes in experience in visual cortex and provide evidence supporting a metaplasticity model of synaptic homeostasis. Together, these presentations will provide diversified views on circuit mechanisms underlying visual function and plasticity.

MONDAY, JANUARY 27, 2020

Monday Morning Panel Sessions

PANEL • MONDAY • 7:30 A.M. - 9:30 A.M. • AMPHITHEATER

Sex Differences in the Effects of Cannabis and Cannabinoid Signaling

Chair: Ryan McLaughlin
Presenters: Aimee McRae-Clark, Elise Weerts, Ryan McLaughlin, Matthew Hill

Important sex differences exist with respect to the behavioral, biological, and clinical effects of cannabis and cannabinoids. Despite a recent increase in the number of studies that include sex as a biological variable, sex differences in the effects of cannabinoids remain understudied, which has limited our understanding of the effects of cannabinoids in females. The participants in this panel will review data from humans and rodent models demonstrating sex differences that render females more vulnerable to the effects of cannabinoids. Aimee McRae-Clark will present data from clinical and human laboratory investigations informing directions for sex-specific treatment development for cannabis use disorder (CUD). Data suggest stress may be an important treatment target for women with CUD. Elise Weerts will present data from studies using positron emission tomography brain imaging to examine type-1

cannabinoid receptor (CB1R) availability in women with CUD compared to nonusers of both sexes. In nonusers, women had higher CB1R availability than men. Women with CUD had lower CB1R availability than women nonusers, which correlated with the subjective effects of cannabis. Next, Ryan McLaughlin will discuss results from preclinical studies employing a novel model of response-contingent cannabis vapor delivery in adolescent male and female rats. Females showed higher rates of responding and experienced sex-specific deficits in cognitive flexibility and white matter development in adulthood. Finally, Matthew Hill will present data on the effects of augmented endogenous cannabinoid signaling on fear extinction in male and female rats. Data indicate that endocannabinoid modulation has a greater impact on fear extinction in female rats that occurs primarily via interactions with TRPV1, as opposed to CB1R. These data reveal significant sex differences in the cannabinoid system, effects of cannabinoids, efficacy of treatment strategies, and their underlying mechanisms of action.

PANEL • MONDAY • 7:30 A.M. - 9:30 A.M. • CANYON

Advancements in Psychedelic Neuroscience

Chair: David Martin
Presenters: David Martin, Natalie Hesselgrave, Cristopher Niell, Katrin Preller

Accumulating clinical evidence suggests that classic psychedelics may have broad therapeutic potential in psychiatry. However, an improved understanding of the multifaceted neural, network, and behavioral mechanisms of psychedelics should help clarify their role in medicine, and this knowledge requires multidisciplinary approaches. This panel's speakers use a variety of techniques (fMRI, calcium imaging, electrophysiology, behavioral) and species (rat, mouse, human) to examine the consequences of psychedelic drug action at multiple levels of inquiry. David Martin (U. Maryland) will open the panel with data demonstrating that the 5-HT2A agonist, DOI, reverses the increased economic demand for an opioid that stems from extended opioid experience in a rat model. Natalie Hesselgrave (U. Maryland) will discuss her studies on the effects of psilocybin in a mouse model of stress induced anhedonia. She will also present data demonstrating the effects of psilocin, a pan-serotonergic agonist, on synaptic activity in hippocampus. Cris Niell (U. Oregon) will present results characterizing neural activity in V1 in response to visual stimuli in awake mice under the influence of DOI. His work utilizes a combination of calcium imaging and silicon probe electrophysiology to measure 5-HT2A effects on cortical processing of visual information, supporting a mismatch between bottom-up and top-down signaling. Katrin Preller (U. Zurich/Yale) will present human behavioral and neuroimaging data acquired after the administration of psilocybin and LSD. These data close knowledge gaps on the neurobiology of psychedelics and their impact on cognition and emotion.

The relevance of these results for psychedelic-assisted treatment approaches will be discussed. In total, this panel highlights the recent developments in 5-HT2A agonist research in diverse basic and applied disciplines, with a focus on mechanistic insight garnered from human and rodent studies.

PANEL • MONDAY • 7:30 A.M. - 9:30 A.M. • CHEYENNE

Fatal Fentanyl: How One Pill Can Kill

Chairs: Phil Skolnick, Irma Cisneros
Presenters: Terrence Boos, Irma Cisneros, Kim Janda, Phil Skolnick

The title of this session paraphrases a paper (Sutter et al., Acad Emerg Med 24:106, 2017) describing the extraordinary measures required to rescue 18 patients hospitalized (one died in hospital) after ingesting tablets adulterated with fentanyl. While the number of opioid overdose deaths appeared to plateau in 2018, fatalities linked to fentanyl (and related synthetics) continue to rise, now surpassing the combined total attributed to prescription opioids and heroin. The panel will discuss both the chemical and pharmacological properties of synthetic opioids that distinguish them from other misused opioids and potential solutions to reduce abuse and overdose deaths. (1) Terrence Boos (DEA) will provide an overview of the illicit manufacturing and trafficking trends of fentanyl and its analogs and the challenges these chemicals pose to drug regulators, including the mutability of the structure, high potency compared to opiates like heroin, and ease of synthesis. (2) Irma Cisneros (UTMB) has discovered the impact of chronic fentanyl self-administration on inflammatory response and innate immunity in the neural circuitry underlying opioid use disorder (OUD). Her data implicate immune targets in brain that may provide novel therapeutic targets to attenuate the chronic impact of OUD. (3) Kim Janda (Scripps) will describe the development of vaccines and monoclonal antibodies directed at fentanyl and related synthetic opioids. The high affinity and specificity of these biologics may be useful for relapse prevention and overdose, while not interfering with standard medication assisted therapies (buprenorphine, methadone). Based on a call in 2017 from NIH leadership to develop "stronger, longer acting opioid antagonists", (4) Phil Skolnick (Opiant) will describe the development of intranasal nalmefene. Structurally related to other opioid antagonists, nalmefene has pharmacological properties that are especially well suited to counteract synthetic opioids like fentanyl.

From Clusters to Stroke Busters: The Cellular, Molecular and Translational Biology of Kv2.1/Neuregulin Complexes

Chair: Elias Aizenman

Presenters: Michael Tamkun, Andres Buonanno, Robert Fyffe, Anthony Schulien

Kv2.1 channels mediate delayed rectifier potassium currents in cortical, hippocampal and spinal motor neurons, regulating neuronal excitability. An additional, non-conducting function of Kv2.1 generates activity-regulated ER/PM (endoplasmic reticulum/plasma membrane) junctions at the neuronal surface by binding to the ER membrane protein VAP. Moreover, neuregulin (NRG), signaling via ErbB4 receptors to modulate synaptic drive and excitability by downregulating NMDARs and Nav channels, tightly associates with Kv2.1 at clusters within the ER/PM junctions. Excitatory activity and injury-mediated changes in phosphorylation status of these proteins dramatically affect Kv2.1 channel trafficking and biophysical function, as well as stimulate shedding of NRG from the cell surface, promoting a wide range of effects on neurons. This panel will discuss the structural, functional and potentially translatable features of Kv2.1/NRG-centered processes, highlighting the diverse roles these proteins play in neuronal function and dysfunction. Elias Aizenman (Pitt) will chair the panel and give brief introductory remarks. Michael Tamkun (Colorado St.) will review the activity-regulated Kv2.1/VAP interaction and then present examples of how the Kv2.1-induced ER/PM contacts regulate calcium homeostasis, membrane protein localization, and exocytosis. Andres Buonanno (NIH) will discuss how NMDAR and NRG/ErbB4 bidirectional signaling can function as a homeostatic mechanism, together with Kv2.1, to protect neurons from excitotoxicity. Robert Fyffe (Wright St.) will discuss the roles and regulation of native Kv2.1 channels and channel clusters at specific post synaptic sites in spinal motoneurons, across a broad range of neuronal activity states. Finally, Anthony Schulien (Pitt) will present the development of a Kv2.1-declustering peptide targeting the channel/VAP association, providing long-term protection from ischemia-reperfusion damage in a rodent model of stroke.

PANEL • MONDAY • 7:30 A.M. - 9:30 A.M. • GALLATIN

Molecular Adaptations Underlying Motivation and Drug-Associated Behaviors

Chairs: Alberto Lopez, Rianne Campbell
Presenters: Alberto Lopez, Megan Fox, Rianne Campbell, Courtney Miller

Substance use disorder (SUD) is a chronic neuropsychiatric disorder fundamentally characterized by dysregulated learning about the rewarding properties of drugs and drug-associated cues. This maladaptive learning manifests in cycles of persistent drug-seeking and drug-taking followed by varying lengths of abstinence and subsequent relapse. Critically, the resilience of drug-seeking behavior is underlined by a long-lasting interplay between altered circuit function and maladaptive regulation of molecular and transcriptional mechanisms. This panel proposal will present original data using multiple novel approaches demonstrating that drugs of abuse recruit molecular and epigenetic mechanisms to drive drug-associated behaviors. First, Dr. Alberto López (Postdoctoral Fellow; Vanderbilt University) will outline epigenetic and proteomic adaptations in the nucleus accumbens recruited throughout cocaine self-administration. Dr. Megan Fox (Postdoctoral Fellow; University of Maryland School of Medicine) will present on fentanyl-induced behavioral and molecular adaptations linked to morphological changes in the nucleus accumbens. Ms. Rianne Campbell (Ph.D. Candidate; University of California, Irvine) will speak on the cell-type specific function of HDAC3, an epigenetic modifier, in regulating cocaine-associated behaviors and cocaine-induced plasticity in the accumbens. Finally, Dr. Courtney Miller (Associate Professor; The Scripps Research Institute) will present new findings on a molecular motor ATPase that remains dynamic long after formation of a methamphetamine-associated memory, enabling selective, retrieval-independent disruption of drug-associated memory and drug-seeking behavior. Together, this session will highlight novel molecular and cellular techniques combined to address the mechanisms underlying behavioral dysregulation in SUD.

PANEL • MONDAY • 7:30 A.M. - 9:30 A.M. • GIBBON

Circuits and Functions of Neurons Defined by Multiple Genetic Characteristics

Chairs: David Root, Marisela Morales
Presenters: Lief Fenno, Susana Mingote, Patricia Jensen, David Root

Advances in the detection of neuronal cell-types suggest that neurons are best defined by multiple, rather than single genetic characteristics. This is especially the case in the ventral tegmental area, where subsets of neurons co-transmit dopamine and glutamate, glutamate and GABA, or singularly release dopamine,

glutamate, or GABA. Cellular diversity has been recognized within the locus coeruleus based on neurotransmitter content as well as developmental progenitors. However, determining the circuits and functions of neurons defined by multiple genetic characteristics has remained challenging. This panel will present novel neurotechnologies and their use to label, record, and control cell-types that are defined by multiple genetic characteristics. Dr. Lief Fenno will describe the engineering, improvement, and characterization of next-generation INTRSECT vectors to control neurons based on the combinatorial presence or absence of multiple recombinases. Dr. Susana Mingote will describe her research on mapping the anatomical and functional connections of dopamine-glutamate neurons in the ventral midbrain and their behavioral functions. Dr. Patricia Jensen will describe her research on a developmentally-specific subset of noradrenergic neurons that when activated, promote a better coping response to acute stress and decrease anxiety-like behavior. Dr. David Root will describe his research on the circuits and behavioral functions of ventral tegmental area neurons that co-transmit glutamate and GABA, release glutamate without GABA, and release GABA without glutamate. Together, this session will demonstrate how multiple recombinase driver lines together with INTRSECT and other newly-developed genetic methods are capable of revealing new insights into how cellular heterogeneity contributes to brain circuitry and cell-type specific function.

PANEL • MONDAY • 7:30 A.M. - 9:30 A.M. • LAKE

Rhythms on the Slope

Chairs: Kamran Diba, Andrew Maurer
Presenters: Lara Rangel, Amy Griffin, Andrew Maurer, Carmen Varela

Network oscillations are considered to reflect intrinsic circuit properties and filtering and coordination between different brain circuits. However, as we approach 100 years of research on these rhythms, their precise nature and relationships to cognition remain to be determined.
During associative memory, the hippocampus must be able to integrate and associate various streams of information. Dr. Lara Rangel performs statistical modeling of rhythmic coordination and shows that associative learning processes depend on coordinated oscillatory activity, and more specifically the engagement of hippocampal cells in distinct rhythmic circuits.
Dr. Amy Griffin explores these questions in spatial working memory (SWM) using multi-site recording from rodents. Exploring functional interactions between the medial prefrontal cortex, the dorsal hippocampus, and the nucleus reuniens during the encoding and retrieval phases of SWM, her study provides insight into the physiological basis of circuit interactions and how they serve behavior.

Dr. Andrew Maurer will present data and analyses on hippocampal theta-gamma coupling. Although the strength of coupling has been related to aspects of memory and cognition, recent data also demonstrate a strong interaction with velocity. His work revisits hippocampal oscillatory organization from the perspective of the 1/f slope and challenges standard dogma regarding "slow gamma".
Dr. Carmen Varela examines the coupling between spindle and sharp-wave ripple oscillations between thalamocortical and hippocampal networks during non-REM sleep, in single units and local field potentials recorded from the midline thalamus, medial prefrontal cortex and hippocampus CA1 of freely behaving rats. She will discuss the functional relevance of the observed dynamics to episodic memory.

PANEL • MONDAY • 7:30 A.M. - 9:30 A.M. • LAMAR

Neuropeptide Signaling Mechanisms: From Molecules to Circuits to Behavior

Chairs: William Giardino, Julia Lemos
Presenters: Jenny He, Julia Lemos, Alexa Veenema, William Giardino

Neuropeptide signaling is critically important for shaping complex behaviors, but efforts to understand neuropeptide transmission have historically been impeded by a lack of tools. For example, neuropeptides are released from dense core vesicles, but the nature, timing, and requirements of release remain elusive. Further, neuropeptides signal via G-protein-coupled receptors, but the diversity of signaling based on sex and cell type is underappreciated. Prior studies using pharmacology and microdialysis indicated that neuropeptides are released by salient changes in internal state or environment. Likewise, earlier evidence suggested that neuropeptides are necessary for stress responsivity, emotional regulation, reward learning and reproductive fitness. However, these studies relied on methods that lacked temporal and/or spatial precision. In addition, many studies focused on general brain areas, whereas there is now recognition of the functional diversity of distinct neuronal populations within regions. Our presentations highlight noteworthy technical advances that have enabled understanding of fundamental neurobiological processes. Specifically, we will discuss novel molecular and genetic tools used in combination with traditional approaches to gain insight into mechanisms of neuropeptide release and signaling across distinct circuits.

Dr. Jenny He (UCSD) will address differences in the mechanisms governing substance P and dynorphin release from striatal direct pathway neurons. Dr. Julia Lemos (U. Minnesota), will discuss how CRF regulates striatal cholinergic interneurons to shape motivated behaviors in male and female mice. Dr. Alexa Veenema (Michigan State) will present on the role of vasopressin in sex- and age-specific regulation of social behaviors. Dr. Will Giardino (Stanford) will

present data on circuit-level interactions between orexin/hypocretin and CRF neuropeptide systems that modulate the stress response and facilitate addiction-like behavior.

Monday Afternoon Panel Sessions

PANEL • MONDAY • 4:30 P.M. - 6:30 P.M. • AMPHITHEATER

Genetic In Vivo Models of Neurological Disease

Chair: Stephen Traynelis
Presenters: Wayne Frankel, Stephen Traynelis, Geoffrey Swanson, Jennifer Kearney

A wide range of neurological diseases appear to involve genetic variation both in single genes and across multiple genes and genetic control elements. In order to understand the mechanism and treatment opportunities for such conditions, generation of in vivo models replicating the genetic alteration are of considerable value. This panel session will focus on in vivo models of neurological conditions that arise from de novo variants in critical individual genes. Dr. Wayne Frankel (Columbia University) will present functional characteristics and interrelatedness for several mouse models of non-ion channel childhood epileptic encephalopathy. Dr. Stephen Traynelis will discuss an in vivo mouse model that contains a de novo GRIN2A missense variant (S644G) identified in pediatric patients showing epileptic encephalopathy and developmental delay. Dr. Geoffrey Swanson (Northwestern University) will describe the behavioral, synaptic and circuit disruptions in a mouse model of a human de novo missense variant in the GRIK2 kainate receptor subunit gene (A657T) that is causative for intellectual disability and ataxia. Jennifer Kearney (Northwestern University) will present in vivo data from mice harboring a missense KCNB1 de novo variant (G379R), derived from a patient with developmental and epileptic encephalopathy. Together these presentations will provide broad background in terms of techniques and approaches, as well as examples of mechanistic advances and potential treatment opportunities for genetically defined neurological diseases.

PANEL • MONDAY • 4:30 P.M. - 6:30 P.M. • CANYON

Striatal Interneurons: Orchestrating Synaptic and Behavioral Adaptations

Chair: Brad Grueter
Presenters: Patrick Rothwell, Anne West, Brad Grueter, Brian Mathur

The striatum, a key component of the basal ganglia, is an essential hub integrating cognitive, contextual, sensory and affective information into behavioral outcomes. While excitatory synaptic connections drive striatal

neuron firing, inhibition and neuromodulation by interneurons are important for coordinating and constraining neuronal excitability. Thus, local microcircuits, particularly parvalbumin fast spiking interneurons and cholinergic interneurons, within the striatum contribute greatly to motivated behavior. In this panel, speakers will discuss the synaptic properties of striatal interneurons and their contribution to behavioral outcomes. Specifically, Patrick Rothwell (University of Minnesota) will discuss interactions between fast-spiking interneurons and medium spiny projection neurons in the nucleus accumbens of male and female mice, during behavioral performance of a 5-choice serial reaction time task. His results suggest fast-spiking interneurons constrain impulsive action in this by inhibiting the output of medium spiny projection neurons. Anne West (Duke University) will share her work identifying the programs of gene expression and chromatin regulation induced in parvalbumin-positive GABAergic interneurons of the nucleus accumbens by exposure to psychostimulants, and she will discuss how this molecular plasticity may alter the synaptic connectivity of these local circuit interneurons. Work presented by Brad Grueter (Vanderbilt University) elucidates a novel mechanism of GluA1 mediated synaptic plasticity at excitatory synapses onto parvalbumin expressing fast spiking interneurons within the nucleus accumbens and the contribution of these receptors to locomotor activation. Brian Mathur (University of Maryland) will present emerging work on a cholinergic interneuron microcircuit in the dorsal striatum and its role in controlling local striatal dopamine release and behavioral reinforcement.

PANEL • MONDAY • 4:30 P.M. - 6:30 P.M. • CHEYENNE

Cannabinoids, Sleep and PTSD: A Bench to Clinic Primer

Chair: Ryan Vandrey
Presenters: Andrew Kesner, Margaret Haney, Ryan Vandrey, Marcel Bonn-Miller

Research has demonstrated a clear impact of cannabis use on sleep, and this relation appears to be particularly relevant among individuals with Cannabis Use Disorder (CUD) and/or Posttraumatic Stress Disorder (PTSD). This panel presentation will provide a translational evaluation of the intersection of cannabinoids, sleep and PTSD. Dr. Kesner will discuss the role of endogenous cannabinoid signaling on sleep stability in mice, and introduce a novel rodent model to elucidate the neural mechanisms and behavioral consequences of THC withdrawal-related sleep disruption. Dr. Haney will discuss the effects of medications on a human laboratory model of cannabis withdrawal and relapse, and will show that improving sleep during withdrawal is necessary but not sufficient for reducing cannabis self-administration following a period of abstinence. Dr. Vandrey will present an outpatient clinical trial in which zolpidem improved sleep during a quit attempt and those receiving zolpidem had clinically meaningful increases in cannabis abstinence, but sleep

dysfunction emerged when zolpidem was stopped. Participants with past trauma and symptoms of PTSD at intake showed improved PTSD symptom scores if they quit cannabis use compared with those who did not quit. Dr. Bonn-Miller will present data from two studies that used both self-report and objective sleep assessments to demonstrate the short- (3 week) and long-term (12 month) effects of cannabinoid use on sleep among individuals with PTSD. Findings suggest a nuanced association between individual cannabinoids and sleep among those with PTSD, which appears to differ from the general population, particularly with respect to long-term outcomes. This session addresses a timely topic, given the widespread legalization of cannabis and hemp, and the integration of pre-clinical, human laboratory, and clinical research on the mechanisms and complexities of how the cannabinoid system affects sleep and health is likely to have broad appeal.

SHORT COURSE • MONDAY • 4:30 P.M. - 6:30 P.M. • DUNRAVEN/OBSIDIAN

Analysis, Visualization and Data Sharing for Human Intracranial Recording and Stimulation

Chair: Michael Beauchamp
Presenters: Kai Miller, Dora Hermes, Dominique Duncan, John Magnotti

One of the fastest growing areas of human neuroscience is electrical recording and stimulation of the human brain via implanted (intracranial) electrodes. This short course will offer a tutorial introduction to these complex datasets. Kai Miller will discuss the basic properties of the iEEG signal. Subsequently, Dora Hermes will illustrate how these data are related to BOLD fMRI data and will discuss what we can learn from each measurement. The Data Archive for the BRAIN Initiative (DABI) fills the unmet need for a shared repository for intracranial data. Dominique Duncan will discuss how DABI offers a streamlined platform for data providers to organize, store, and manage multimodal datasets, including clinical, demographic, imaging, electrophysiology, and pathology data. Finally, John Magnotti will demonstrate common iEEG analysis techniques using a purpose-built open-source tool, R Analysis and Visualization of intracranial EEG data (RAVE).

PANEL • MONDAY • 4:30 P.M. - 6:30 P.M. • GALLATIN

It's all Downhill From Here: Dopamine Function and Dysfunction in Movement Initiation

Chairs: Elyssa Margolis, Leslie Sombers
Presenters: Jakob Dreyer, Mark Howe, Alexandra Nelson, Leslie Sombers

Action initiation is a critical timepoint in an organism's response to contexts and cues. Experimentally, it is often interpreted as the time of decision. Many neural circuits implicated in encoding decisions are also intensely studied for their role in action initiation. This is the case in the dorsal striatum, and in the investigation of dopamine (DA) function therein. In this panel, we will explore new understanding of striatal function in action initiation, in both healthy and dysfunctional states. Margolis will briefly introduce context for the session. Dreyer will discuss new insights into basal ganglia function based on computational modeling with a focus on the role of DA cell firing in the generation of DA transients in the dorsal striatum. Howe will present recent, unpublished work investigating patterns of striatal DA and acetylcholine (Ach) signaling on multiple spatial and temporal scales in behaving mice. They find functional heterogeneity on scales from 10s of microns to millimeters and a dynamic coordination of DA and Ach signaling that varies with behavioral state. Dysfunction of striatal circuits is thought to critically contribute to unwanted spontaneous movements, for example in levodopa-induced dyskinesias in long-term treatment of Parkinson's disease. Nelson will describe a novel subset of dyskinesia-related striatal neurons, identified by activity-dependent capture of neurons in a levodopa-induced dyskinesia model. These neurons differ in the changes in excitatory synaptic inputs and intrinsic excitability compared to uncaptured, neighboring neurons. Finally, in the same model of dyskinesia, Sombers will describe unpublished findings on the fluctuations in striatal hydrogen peroxide and dopamine, and how these fluctuations relate to abnormal movement. Together, these talks will provide updated perspectives on the function and dysfunction of dopamine-dependent striatal signaling in the context of movement.

PANEL • MONDAY • 4:30 P.M. - 6:30 P.M. • GIBBON

Linking Endocytosis to Neuronal Survival

Chair: Elizabeth Jonas
Presenters: J. Marie Hardwick, Leonard Kaczmarek, Elizabeth Jonas, Zhenyu Yue

The process of endocytosis leads either to the recycling of membrane proteins or to the subsequent destruction of the retrieved proteins. The latter process is linked to the formation of late endosomes or autophagosomes. This panel will discuss work that has revealed some molecular links that determine the

fate of internalized membranes, including synaptic vesicles. Marie Hardwick will discuss the role of KCTD (potassium channel tetramerization domain) proteins, which share domains with plasma membrane potassium channels but are not themselves ion channels. Mutations in KCTD family members are responsible for severe neurodevelopmental disorders, and one of these, KCTD7, has been found to regulate an autophagy-lysosome pathway in neurons. Len Kaczmarek will describe how a presynaptic potassium channel is required for normal endocytosis of synaptic vesicles. Human mutations in this channel trigger abnormal endocytosis and produce neuronal death linked to the trafficking of cell survival proteins into late endosomes and exosomes. Elizabeth Jonas will describe how an anti-cell death protein, Bcl-xL and possibly also the Parkinson's protein DJ-1 enhance endocytosis to increase the size of the neurotransmitter-containing vesicle pool and how these proteins make trafficking decisions during presynaptic plasticity. Zhenyu Yue will speak about how presynaptic trafficking protein Synaptojanin 1 is regulated by LRRK2 kinase, which is linked to the most common familial form of Parkinson's disease (PD). Phosphorylation of Synaptojanin 1 by LRRK2 disrupts endocytosis selectively in dopaminergic neurons. He will describe how SYNJ 1 haploinsufficiency contributes to synaptic vesicle endocytosis impairment, age dependent autophagy deficiency, alpha-synuclein accumulation, axon degeneration and abnormal locomotor function in mice. He finds through analysis of PD postmortem brains, that Synaptojanin 1 reduction may contribute to the pathogenesis of PD.

PANEL • MONDAY • 4:30 P.M. - 6:30 P.M. • LAKE

New Developments on Hypothalamic and Brainstem Control of Defensive Behaviors

Chair: Avishek Adhikari
Presenters: Sung Han, Jaideep Bains, Jason Radley, Avishek Adhikari

Innate threats arise from various sources, including predators, asphyxiation and pain. Understanding the neural circuits that coordinate reactions to these events is vital for understanding both adaptive behaviors as well as related pathological symptoms, such as panic attacks. We will explore how reactions to innate threats are orchestrated by hypothalamic and brainstem circuits.
Dr. Adhikari will briefly discuss the panel's theme, introduce the speakers and moderate questions. First, Dr. Han will show that activity in calcitonin gene related-peptide –expressing neurons in the parabrachial nucleus controls the physiological and behavioral symptoms elicited by numerous panicogens in mice. Dr. Bains will show that in mice the escape elicited by a looming disk is preceded by an increase in the activity of hypothalamic CRH-PVN neurons (CRH-PVN). This anticipatory increase in activity is sensitive to stressful stimuli that have high or low levels of outcome control. These observations

indicate that CRH-PVN decode stress controllability and contribute to shifts between active and passive innate defensive strategies. Dr. Radley will then show that in rats the projections from the medial prefrontal cortex to dorsal or ventral periaqueductal gray (dPAG and vPAG) respectively control passive and active defensive behaviors elicited by a shock probe, showing how distinct cortical-PAG projections dynamically modulate threat-elicited defensive strategies. Lastly, Dr. Adhikari will discuss how the projection from cholecystokinin-expressing cells in the posterior hypothalamus to the periaqueductal gray controls escape induced by numerous innate threats. Interestingly, this circuit can elicit organized escape through the most optimal escape route available in geometrically complex environments.
Taken together, these data highlight the diverse and critical roles played by evolutionarily conserved circuits in the hypothalamus and brainstem during exposure to innate threats of multiple modalities.

PANEL • MONDAY • 4:30 P.M. - 6:30 P.M. • LAMAR

Structural, Functional and Molecular Mechanisms of Dendritic Spine Plasticity

Chair: Yi Zuo
Presenters: Yi Zuo, Kristen Harris, Ryohei Yasuda, Jason Shepherd

Dendritic spines are the postsynaptic sites of most excitatory synapses. Their structures and functions are regulated by experiences through a complex network of molecular signals. The abnormal density and morphology of spines are hallmarks of many neurological and psychiatric disorders. This panel will focus on structural and functional plasticity of dendritic spines under both physiological and pathological conditions. It will also discuss molecular and local circuit changes underlying spine plasticity. Dr. Yi Zuo (University of California Santa Cruz) will give an overview of dendritic spines and their plasticity, and discuss in more detail the spine calcium activity during motor skill learning and motor performance. Dr. Kristen Harris (University of Texas at Austin) will discuss changes in resource distribution underlying hippocampal long-term potentiation that determine where dendritic spines cluster and protect their smaller neighbors. Dr. Ryohei Yasuda (Max Planck Florida Institute for Neuroscience) will discuss the spatiotemporal dynamics of postsynaptic signals underlying the growth and long-term potentiation of single dendritic spines. Finally, Dr. Jason Shepherd (University of Utah) will present his discovery of a novel intercellular communication mediated by Arc signaling that describes the structure and potential function of Arc virus-like capsids. The panel will conclude with discussion and questions.

Special Session

SPECIAL SESSION • MONDAY • 7:00 P.M. - 8:30 P.M. • AMPHITHEATER

Improving the Climate in Scientific Disciplines

Chair: Jill Becker

Presenters: Kathryn Clancy, Paul Phillips, Jonathan Morrow, Carrie Ferrario

Overwhelming research has documented that sexual harassment happens in the sciences; that contemptuous behaviors like gender harassment are the most common; and that current measures intended to decrease harassment prevalence over the last thirty years have failed. Sexual harassment has profound consequences, personally and professionally, for individual targets as well as the broader climate of science. A recent National Academies consensus report has documented these findings and others, and made substantial recommendations for change. For specific scientific disciplines to remain relevant they must engage directly with these data and recommendations.

This session will provide an overview of the research on sexual harassment and the main findings of the National Academies report, led by report co-author and scientist Dr. Kathryn Clancy. Dr. Clancy will then lead a mini-workshop on the ways in which individuals, research groups, and professional societies can create inclusive practices that reduce tolerance for harassment. Jill Becker and Paul Phillips (past WCBR conference chairs) will be joined by Carrie Ferrario and Jonathon Morrow to facilitate the workshop session. This workshop is not intended as a therapeutic space, nor will it be one where participants will be encouraged to share personal stories. This is to keep targeted people safe who may not otherwise be able to participate in a workshop like this. We also recognize that discussions of this type can trigger unwanted memories or feelings, so we counsel self-care throughout the session. Please join us to show support for the cause of making WCBR a place where everyone can participate in scientific discourse without restrictions.

Brain Talk Town Meeting

PLENARY • MONDAY • 7:00 P.M. - 8:30 P.M. • GALLATIN

The Transparent Time Window: A New Perspective on Stroke Treatment

Presenter: Gregory Albers

The last 2 years have seen extraordinary advances in stroke treatment. Two large clinical trials, that used automated software developed at Stanford University to identify patients who have slowly evolving strokes were published in the New

England Journal of Medicine. The goal of these trials was to expand the stroke treatment window from a 6-hour limit up to 24 hours. This was accomplished by determining how quickly the stroke was growing at the time the patient arrived at the hospital and treating patients who still had salvageable tissue with a mechanical device that removes the blood clots from the brain. Both trials were stopped early because of overwhelming success. In DEFUSE 3 the rate of severe disability or death was cut in half and in DAWN the rate of functional recovery from the stroke was more than tripled.

In essence, modern imaging techniques have made the stroke treatment window transparent for individual patients which allow therapy to be tailored based on the specific characteristics of each stroke. These advances have led to an entirely new approach to evaluating and treating stroke patients which has already been adopted in over 40 countries.

TUESDAY, JANUARY 28, 2020

Tuesday Morning Panel Sessions

PANEL • TUESDAY • 7:30 A.M. - 9:30 A.M. • AMPHITHEATER

Broadening the Neural and Associative Mechanisms of Fear

Chair: Melissa Sharpe
Presenters: Joshua Johansen, Melissa Sharpe, Stephen Maren, Moriel Zelikowsky

Fear research has traditionally focused on the amygdala, thought to receive low-level information to coordinate a behavioral response to fearful stimuli. However, as our understanding of the associative mechanisms of fear have evolved, so too has our knowledge of the neural substrates underlying fear. Our panel will discuss recent findings that point to unexpected players in fear circuitry. First up, Joshua Johansen will identify a novel glutamatergic mesencephalic reticular formation pathway involved in fear learning, which integrates aversive sensory and defensive behavioral response information to trigger fear learning through direct projections to lateral amygdala. This pathway is critical to fear circuits; inactivation abolishes fear learning and reduces shock evoked responding in amygdala. Secondly, Melissa Sharpe will demonstrate that the lateral hypothalamus- a region thought to contribute exclusively to feeding- becomes necessary for fear learning after a history of learning about rewards. This is accompanied by a decrease in activity in basolateral and central amygdala, suggesting a shift in the neural substrates encoding fear. Then, Stephen Maren will uncover a novel prefrontal-thalamic circuit involved in the regulation of fear after threat has passed. Specifically, Stephen will show inactivation of the nucleus reuniens, or its afferent from prefrontal cortex,

increases fear and prevents recruitment of hippocampal circuits necessary for fear extinction. Finally, Moriel Zelikowsky will discuss the involvement of Tachykinin2 (Tac2) in the persistent fear that accompanies chronic social isolation stress. She will show that Tac2 is upregulated throughout the brain in this model, and is necessary and sufficient for this persistent fear, with particular relevance to PTSD. Together, this research reveals new substrates regulating fear memories, providing an avenue for pre-clinical work aimed at treating anxiety disorders characterized by maladaptive fear.

PANEL • TUESDAY • 7:30 A.M. - 9:30 A.M. • CANYON

Gene and Protein Networks in Autism and Schizophrenia

Chairs: Stephen Smith, Dan Geschwind
Presenters: James Knowles, Dan Geschwind, Stephen Smith, Lilia Iakoucheva

Neuropsychiatric disorders show enormous phenotypic and genetic heterogeneity, but individual implicated genes are pleiotropic, affecting many cellular functions simultaneously. Sorting pathogenic molecular pathways from irrelevant or compensatory changes continues to be a challenge. In this panel, we will discuss recent advances in our understanding of the gene and protein networks implicated in neuropsychiatric disorders.

James Knowles will describe his group's work on a collection of 255 genetically unmodified neural progenitor cell lines derived from individuals with, and without, schizophrenia (SCZ). The genes identified by differential expression (DEX) analyses in these lines are significantly enriched in peaks in the PGC2 SCZ GWAS. A large number of DEX genes are involved in WNT5A signaling and 20-40% of individuals with SCZ may have alterations in this pathway.

Dan Geschwind will speak about his group's latest work, single nucleus sequencing in ASD cerebral cortex using the 10x genomics platform. Their previous work using whole tissue-based profiling showed specific patterns of gene dysregulation in about 2/3 of cases that implicated an up-regulation of microglia and astrocytes, and a down-regulation of specific neuronal programs. These single nucleus data from the largest cohort to date (>30 cases and controls), and further refine this pattern to include specific cell types and states in ASD.

Stephen E.P. Smith will speak about his group's work using the quantitative multiplex co-immunoprecipitation platform to model intracellular signal transduction pathways at the glutamate synapse. His talk will describe how protein interaction network states are disrupted in ASD, and how these disruptions alter the neuronal response to synaptic activity.

Lilia Iakoucheva will speak about using ASD patient-derived cerebral organoids and CRISPR animal models to identify differentially expressed genes, proteins and co-expression modules impacted by ASD mutations.

PANEL • TUESDAY • 7:30 A.M. - 9:30 A.M. • CHEYENNE

Neurobiological Mechanisms Underlying the Potential Therapeutic Effects of Psychedelics

Chair: Melissa Herman
Presenters: Mark Geyer, Samuel Slocum, William Wetsel, Harriet de Wit

Psychedelics are broadly classified as psychoactive compounds that alter perceptions, elicit hallucinations, and/or impact affective states. Recent research has highlighted the potential of these compounds in a number of therapeutic applications, including treatment for depression, anxiety, and addiction. Due to restrictive DEA scheduling, however, our understanding of the signaling mechanisms and circuitry associated with the activity of psychedelic compounds is incomplete. This panel will provide new perspectives on the neurobiological actions of psychedelics by emphasizing molecular mechanisms associated with signaling, cell type-specific actions in relevant brain regions, and relevant behavioral paradigms. Dr. Melissa Herman (University of North Carolina, Chapel Hill) will provide a brief introduction and lead the discussion. Dr. Mark Geyer (University of California, San Diego) will review the recent history and current status of the resurgence of interest and research regarding the potential clinical applications of psychedelics such as psilocybin. Dr. Samuel Slocum (University of North Carolina, Chapel Hill) will present his work screening the "hallucinome", elucidating the receptors and signaling pathways employed by psychedelics. Dr. William Wetsel (Duke University) will present his studies investigating the role of β-arrestins in the behavioral effects of LSD in mice. Finally, Dr. Harriet de Wit (University of Chicago) will present new data on the effects of LSD microdoses on EEG measures of emotional reactivity and reward in healthy human volunteers. As the cultural significance, clinical relevance, and therapeutic potential of psychedelic compounds are only increasing, it is important to improve our understanding of the complexity and diversity of their biological actions. This panel will introduce new results highlighting recent advances in our understanding of the neurobiological mechanisms mediating the behavioral effects of psychedelic drugs.

WORKSHOP • TUESDAY • 7:30 A.M. - 9:30 A.M. • DUNRAVEN/OBSIDIAN

Educating the Next Generation: Innovative Approaches to Make Science Fun

Chairs: Lloyd Fricker, Sybil Stacpoole
Presenters: Ronald Harris-Warrick, Matt Carter, Karen Greif, Bradley Tanner

Today's students have grown up using the internet, and teaching approaches that worked for previous generations are no longer effective. Alternative teaching approaches are also important to expand the diversity of students

choosing careers in science and technology. This workshop will highlight innovative techniques using active learning approaches that make science education enjoyable and improve learning. Using the workshop format, each speaker's presentation will be brief in order to allow for extensive discussion. Presentations will include metrics for assessing whether the novel active learning approaches are effective.
The session will be moderated by Lloyd Fricker (Einstein College of Medicine), who has developed team-based learning in a medical school curriculum, and by Sybil Stacpoole (University of Cambridge) who brings experience with the Oxbridge small group supervision system, an early example of active learning adapting to modern times. Ron Harris-Warrick (Cornell U.) will describe a variety of active learning-based approaches to enhance scientific creativity that have been successful in undergraduate and graduate courses in a large university setting. Matt Carter (Williams College) will describe approaches for increasing active learning in science at a small liberal arts college environment. Karen Greif (Bryn Mawr College) will discuss the incorporation of science ethics and policy in courses for undergraduates as a way to make the concepts more relevant to the students. Brad Tanner (Clinical Tools, Inc.) will describe a virtual reality headset and computer programs for neuroscience education, from grade schoolers to clinicians. In addition to the above presentations, ample time will be provided for attendees to describe innovative ideas that they have used in their teaching.

PANEL • TUESDAY • 7:30 A.M. - 9:30 A.M. • GALLATIN

Sex Differences in Opioid Use and Outcomes: From Synapses to Circuits

Chairs: Matthew Hearing, Eden Anderson
Presenters: Anne Murphy, Beverly Reyes, Suman Guha, Eden Anderson

Even when taken as prescribed, opioid use carries significant risk for misuse, dependence, and addiction. The incidence of reported heroin use and nonmedical prescription opioid use is on the rise in recent years, however the rate at which women are using heroin has increased to a greater extent. Until advances are made towards filling knowledge gaps regarding neurobiological sex differences -- both intrinsic and drug-induced -- that influence how each sex responds to both initial and prolonged opioid exposure, progress towards developing more targeted and impactful therapies will remain hindered. Presenting mostly unpublished data, this diverse panel of investigators will discuss data demonstrating sex-related overlapping and divergent effects of opioids on drug intake and affective behavior, neuronal physiology, and receptor signaling from the synapse to circuits and beyond. Dr. Anne Murphy will be presenting data on the impact of biological sex and age on morphine analgesia and the role of neuroimmune signaling. Dr. Beverly Reyes will

present data on the effect of chronic morphine on the subcellular distribution of mu opioid receptor and corticotropin-releasing factor type 1 receptor in the locus coeruleus of male and female rats using immunoelectron microscopy. Dr. Suman Guha will present data showing the characterization of oxycodone self-administration and withdrawal-associated negative affect in male and female rats by utilizing concurrent intracranial self-stimulation, intravenous self-administration, and data-driven behavioral analysis. Dr. Eden Anderson will present data on sex-specific medial prefrontal cortex and nucleus accumbens plasticity following opioid self-administration in male and female mice and the role this plasticity has on cognitive flexibility.

PANEL • TUESDAY • 7:30 A.M. - 9:30 A.M. • GIBBON

Crossed Wires and Dissolving Priors: State-Dependent Changes in Connectivity Within the Cortico-Thalamic Network

Chair: Matthew Banks
Presenters: Matthew Banks, Katrin Preller, Anthony Hudetz, Stefanie Blain-Moraes

Current theories of brain function rely on bidirectional message passing within the cortico-thalamic network, but the explicit roles of feedback and feedforward pathways in perception and cognition remain unclear. Understanding how connectivity changes with arousal state will elucidate these roles. Panelists will present data from recent investigations focusing on sleep, disorders of consciousness, anesthesia and psychedelic states. Matthew Banks (Univ. Wisconsin) will present an overview of connectivity metrics, using data from human subjects that relate structural, functional and effective connectivity measures to explore common mechanisms of loss of consciousness under sleep and anesthesia. Katrin Preller (Univ. Zurich/Yale Univ.) will present data on changes in functional and effective connectivity in altered states of consciousness induced by psychedelics such as psilocybin and LSD in human participants, focusing on the relevance of these changes for understanding the mechanism of action of psychedelics and their induced subjective effects. Anthony Hudetz (Univ. Michigan) will speak about recurrent neuronal interactions in rodent visual cortex, extending earlier findings on long-range feedforward and feedback connectivity. He will discuss state-dependent local communication of neuron populations as modulated by anesthetics and analyzed by information theoretic measures. Stefanie Blain-Moraes (McGill Univ.) will speak about patterns of feedforward and feedback connectivity in individuals with disorders of consciousness, focusing on experiments using anesthesia to perturb the brain networks of these patients. She will demonstrate how patterns of spurious feedback connectivity can arise in some patients, and emphasize the need to test the dynamic properties of functional

connectivity patterns. The panel will foster better understanding of the role of cortical recurrent connectivity in the healthy waking brain and in relevant neuropsychological conditions.

PANEL • TUESDAY • 7:30 A.M. - 9:30 A.M. • LAKE

Stability and Plasticity in Hippocampal and Cortical Networks

Chair: Kamran Diba

Presenters: Sebastien Royer, Gideon Rothschild, Kamran Diba, Andrew Maurer

To support adaptive behavior, the brain must balance stability and plasticity. Yet how the functional organization and dynamics of neuronal ensembles change with behavioral state, time and experience is poorly understood. Our panel examines this question from a variety of angles.

First, Sebastien Royer will discuss how place cells in the dentate gyrus of the hippocampus generate spatially selective firing fields that map the continuum of positions in environments. He will present experimental and theoretical evidence revealing that dentate granule cells progressively develop single evenly dispersed place fields via competitive learning and the integration of object-vector cell and grid cell inputs, thus encoding the specific layout of objects in a novel context.

Next, Gideon Rothschild will present his work based on two-photon calcium imaging of identified neuronal ensembles in the auditory cortex of behaving mice across multiple days of exposure to stimuli. The results suggest an unexpectedly high degree of plasticity in ensemble-level sound representations in the cortex.

Kamran Diba will discuss the rapid spiking response of hippocampal neurons both local and distal to focal optogenetic suppression and excitation. Findings indicate unexpected firing increases and decreases in CA3 that are transferred to downstream targets in region CA1. These observations are largely consistent with inhibitory-stabilization, a frequent motif in hippocampal-cortical networks.

Finally, Andrew Maurer will present simultaneous recordings of local field and ripple oscillations from the CA1 and CA3 hippocampal subregions of young (4 month) and aged (24 month) rats. Preliminary data showed that the probability of CA3-CA1 ripple co-occurrence is decreased in aged animals, suggesting that the aged CA3 has decreased influence over CA1.

We conclude with an open discussion of the collective implications of these findings for the dynamics of neuronal populations through adulthood.

PANEL • TUESDAY • 7:30 A.M. - 9:30 A.M. • LAMAR

Glutamate Receptors: From Structure to Function

Chairs: Johannes Hell, R. Suzanne Zukin
Presenters: R. Suzanne Zukin, Sabine Spijker, August Smit, Johannes Hell

Most synapses in the brain use glutamate as neurotransmitter. Basal synaptic transmission is mostly mediated by Na influx through AMPARs whereas Ca influx through NMDARs leads to synaptic plasticity. Many mental and neurological disorders are due to dysregulation of glutamate receptor function. This panel is co-chaired by Suzanne Zukin, who will give the introduction to glutamate receptor function, and Johannes Hell. Our panel will evaluate different aspects of the composition and cell biology of glutamate receptors and their regulation and function. Talks span from the role of NMDAR regulation by PKA to mechanisms that anchor AMPARs at postsynaptic sites and their role in synaptic plasticity. Suzanne Zukin will discuss new findings that loss of the PKA phosphorylation site of the NMDAR GluN2B subunit impairs forms of synaptic plasticity that require the transient insertion of Ca2+ permeable AMPA receptors at CA1 synapses and cognition, as assessed by novel object recognition and contextual fear conditioning. Sabine Spijker will discuss the role of the secreted glycoprotein Noelin1 in inhibiting AMPAR lateral mobility and how that contributes to synaptic plasticity. August (Guus) Smit will talk about how members of the family of the Shisa (or CKAMP) auxiliary AMPAR subunits regulate functional availability of AMPAR at postsynaptic sites. Finally, Johannes Hell will present data on the role of alpha-actinin in anchoring PSD-95 and with it AMPARs at the postsynaptic site.

PANEL • TUESDAY • 7:30 A.M. - 9:30 A.M. • TALUS

Heterogeneity of Midbrain VTA/SNc Cells and the Properties Underlying Diversity of Neurotransmission

Chair: Chris Ford
Presenters: Sarah Zych, Vivien Zell, Jorge Miranda-Barrientos, Louis-Eric Trudeau

The ventral tegmental area (VTA) and substantia nigra compacta (SNc) are comprised of a variety of neurons than can release and co-release dopamine, glutamate and GABA. In this panel speakers will discuss recent work examining the heterogeneity of these different neurons, the mechanisms which control the synaptic release of their transmitters, and the differing roles these cells play in regulating reward processing. Sarah Zych (University of Colorado) will present data examining the properties of the synaptic co-release of dopamine and GABA from midbrain dopamine neurons onto striatal medium spiny neurons. By simultaneously measuring synaptic activation of D2-receptors and GABAA receptors she will discuss how the co-release of these two transmitters

is regulated at striatal synapses. Vivien Zell (UCSD) will discuss the relative contribution of VGluT2-expressing (glutamate) neurons in the reinforcing properties of the VTA. A subpopulation of VTA glutamate neurons is able to co-release dopamine. Dr Zell has isolated glutamate transmission (absent of dopamine release) to determine the role this population in reward processing. Jorge Miranda Barrientos (NIDA) will talk about the diversity in the electrophysiological properties of VTA neurons that co-express VGluT2 and VGaT (glutamate-GABA neurons), neurons that express VGluT2 but not VGaT (glutamate-only), and neurons that express VGaT but not VGluT2 (GABA-only). He will discuss characterization of these cells that has allowed them to selectively label the different phenotypes of neurons. Louis-Eric Trudeau's (University of Montreal) research focuses on the axonal connectivity of dopamine neurons. In his presentation, he will present some of his recent work on the synaptic and non-synaptic connectivity of dopamine neurons and on the organization and regulation of glutamate synapses formed by these neurons.

Pioneer Session # 2

PIONEER SESSION • TUESDAY • 9:45 A.M. – 11:00 A.M. • AMPHITHEATER

More than 50 Years at WCBR – Brain Reward, Dopamine, the D3 Receptor, Atypical Dopamine Transport Inhibitors, and Cannabinoids

Pioneer: Eliot Gardner
Chair: Amy Newman
Investigators: Andrea Hohmann, Zheng-Xiong Xi

My first attendance at WCBR was in 1968 – the founding year of the conference. My early work was on brain reward and dopamine's involvement in it. The next major research that occupied my time and attention was work on the dopamine D3 receptor, and the very real possibility that highly selective D3 receptor antagonists may have broad anti-addiction efficacy in a wide range of preclinical animal models – work that continues to the present day. Work on atypical dopamine transport (DAT) inhibitors as potential anti-addiction medications followed, and continues to the present day. My attention was then grabbed by cannabinoids and the endocannabinoid systems – with extensive study of selective cannabinoid CB1 receptor antagonists and selective CB2 receptor agonists as potential anti-addiction, anti-craving, anti-relapse medications. Recently, my lab has been studying the tetrahydrocannabivarins as potential anti-addiction, anti-craving, anti-relapse medications – with extremely promising results. It is astounding to me to look back over the 50 years and realize how very little we knew about the brain and behavior in 1968, how far we have come, and how far we still need to go.

Career Development Session # 2

SPECIAL SESSION • TUESDAY • 2:00 P.M. – 3:30 P.M. • CHEYENNE

Tips and Tools for Success in Academia

Chair: Lakshmi Devi
Participants: Kyle Frantz, Stephanie Borgland, Lloyd Fricker

This is a career development session focusing on "Tips and Tools for Success in Academia". The session is geared towards senior graduate students, postdoctoral fellows and junior investigators, but open to scientists at all stages of their career. Lakshmi Devi (Icahn School of Medicine at Mount Sinai) will chair this session. The panelists include Kyle Frantz (Georgia State University), Stephanie Borgland (University of Calgary) and Lloyd Fricker (Albert Einstein College of Medicine). The choice of topics will be driven by the audience, and will potentially include topics such as resolution of conflicts (between lab personnel; data interpretation; manuscript authorship; work/life balance), initiating and handling difficult conversations, setting up successful collaborations, and the importance of mentoring. Audience participation will be encouraged, both to raise topics for discussion as well as to contribute to the discussion.

Tuesday Afternoon Panel Sessions

PANEL • TUESDAY • 4:30 P.M. - 6:30 P.M. • AMPHITHEATER

The Highs and Lows of GABAergic Transmission in Anxiety: Reconciling Contradictory Findings From Rodents and Humans Studies

Chair: Laurence Coutellier
Presenters: Elif Engin, Elizabeth Lucas, Laurence Coutellier, Georg Oeltzschner

A deep mechanistic understanding of the underlying biology of anxiety disorders remains a "task in progress". The majority of preclinical and clinical studies agree on abnormal GABAergic transmission as an underlying mechanism of fear and anxious behaviors. However, there is a lack of consensus on the direction of these changes in inhibitory transmission, as well as their contribution to the heterogeneous symptoms of anxiety disorders. The goal of this panel is to provide a much needed biologically-based understanding of the relationship between anxious behaviors and GABAergic abnormalities. We will discuss factors that could underlie divergent findings, including brain region, sex, and age based on state-of-the-art approaches in rodents and humans. Dr. Engin will discuss findings in conditional knockout mice showing that

hippocampal α2-containing GABAA receptors in CA1, CA3, and the dentate gyrus each regulate only specific types of defensive behaviors rather than being involved in anxiety-like behaviors unselectively. Dr. Lucas will talk about how puberty onset and cycling gonadal hormones confer women's susceptibility to anxiety disorders. Her data highlight amygdala parvalbumin interneurons as a hormone-sensitive cellular substrate driving sex differences in mice emotional behaviors. Dr. Coutellier will summarize data obtained using DREADD and transgenic mice showing prefrontal over-inhibition as a mechanism underlying anxiety-like behaviors in females. Finally, Dr. Oeltzschner will present human in vivo magnetic resonance spectroscopy (MRS) data and discuss the interpretation of the MRS GABA signal in the context of anxiety. Altogether, we will provide novel perspectives into GABAergic disturbances in fear and anxiety in an effort to synergize convergent findings and to reconcile contradictory ones. We hope to start a discussion that will provide a rationale platform for the development of novel therapeutic strategies for those affected by an anxiety disorder.

PANEL • TUESDAY • 4:30 P.M. - 6:30 P.M. • CANYON

Recent Insights Into the Neurobiological Mechanisms Underlying Opioid Self-Administration and Reinstatement

Chair: David Reiner

Presenters: Marsida Kallupi, Heath Schmidt, Jennifer Fragale, David Reiner

The current opioid crisis is fueled by use of and relapse to both prescription and illicit opioids, particularly oxycodone and fentanyl. However, few preclinical studies have investigated the neurobiological mechanisms underlying self-administration and reinstatement to oxycodone or fentanyl. Based on this gap in knowledge, we present recent findings exploring the behavioral and neurobiological mechanisms of oxycodone and fentanyl self-administration and reinstatement. Marsida Kallupi (UCSD) will present data on the role of nociceptin in oxycodone self-administration and reinstatement. Marsida will demonstrate that central amygdala injections of small molecules that target the N/OFQ system decrease oxycodone self-administration and reinstatement in dependent rats. Heath Schmidt (Penn) will discuss findings on the role of glucagon-like peptide-1 (GLP-1) in oxycodone self-administration and reinstatement. Heath will present data showing that systemic injections of a GLP-1 receptor agonist selectively reduce oxycodone self-administration and reinstatement without compromising antinociception, effects which are mediated, in part, by activation of GLP-1 receptors in nucleus accumbens shell. Jennifer Catuzzi Fragale (Rutgers) will present findings on the role of orexin in fentanyl self-administration. Jennifer will present data showing that intermittent-access to fentanyl induces a robust 'addiction-like' state that is mediated by long term changes in the orexin system. David Reiner (NIDA)

will describe new findings on the role of the orbitofrontal cortex in a rat model of fentanyl relapse after contingency management. David will present data showing that inactivation of orbitofrontal cortex decreases fentanyl seeking after food choice-induced voluntary abstinence without affecting drug taking during reacquisition. Collectively, this panel will highlight novel behavioral and neurobiological mechanisms underlying opioid self-administration and reinstatement.

PANEL • TUESDAY • 4:30 P.M. - 6:30 P.M. • CHEYENNE

New Advances in Understanding of Orexin/Hypocretin in Addiction: Converging Evidence From Physiological and Behavioral Models in Multiple Species

Chairs: Morgan James, William Giardino
Presenters: Brooke Schmeichel, William Giardino, Morgan James, Sarah Leibowitz

Lateral hypothalamus neurons containing the neuropeptide hypocretin/orexin are essential for guiding diverse forms of motivated behavior, including drug-seeking. However, our understanding of this system in addiction has been impeded by the immense heterogeneity of hypocretin/orexin neurons. This panel captures recent noteworthy methodological advances enabling us to unravel fundamental processes of the hypocretin/orexin system in motivated behavior. We will present unpublished data from studies using novel behavioral, physiological, and genetic approaches in combination with traditional methods to gain insight into neural circuit mechanisms of hypocretin/orexin action in addiction.

Dr. Schmeichel (NIDA) will address a role for hypocretin/orexin in negative reinforcement and sleep disturbances during acute withdrawal in alcohol dependence. Dr. Giardino (Stanford) will present data on circuit-level interactions between the extended amygdala and the hypocretin/orexin system that facilitate binge alcohol drinking and addiction-related behaviors. Dr. James (Rutgers) will describe evidence that plasticity in the number of hypocretin/orexin neurons underlies addiction to several drugs of abuse, and show evidence supporting the repurposing of the FDA-approved dual hypocretin/orexin receptor antagonist suvorexant for the treatment of addiction. Finally, Dr. Leibowitz (along with her postdoc Adam Collier, Rockefeller) will present evidence from both rodent and zebrafish models indicating that early ethanol exposure alters the density, migration and anatomical location of hypocretin/orexin cells, and that these changes are associated with altered addiction-like behaviors.

Obesity and the Regulation of Body Weight – It's Not All in Your Head

Chairs: Carrie Ferrario, Lloyd Fricker
Presenters: Kevin Williams, Lloyd Fricker, Darleen Sandoval, Ian Willis

Traditionally, energy balance has been thought to be largely controlled by the brain. Within the hypothalamus, key circuits in the regulation of body weight are thought to include neurons expressing neuropeptide Y (NPY) which stimulates feeding, and neurons expressing proopiomelanocortin (POMC) which reduces feeding. However, the regulation of energy balance and body weight are more complex. After a brief introduction by Carrie Ferrario (U Michigan), Kevin Williams (UT Southwestern) will present recent work examining how obesity and exercise alter POMC and NPY/AgRP neuron function within the hypothalamus. These data support a rapid reorganization of cellular properties in response to exercise, and hold intriguing possibilities to facilitate adaptations to alter energy balance and glucose metabolism. Lloyd Fricker (Einstein College of Med) will describe recent work with mice lacking carboxypeptidase E, a major neuropeptide-producing enzyme. Whereas mice with a global knockout of CPE are severely obese, conditional knockout mice that lack CPE only in POMC-expressing neurons are a normal weight, indicating that the phenotype of the global CPE knockout is not due to alterations in POMC-derived peptides. Darleen Sandoval (U Michigan Med Schl) will present work examining adaptations of the gut-brain axis after bariatric surgery and the potential mechanistic role of these adaptations in the profound weight-loss and improvements in glucose and lipid homeostasis seen with these surgeries. In particular, she will discuss the roles of neuropeptides secreted from the gut and hindbrain circuits that drive the metabolic success of surgery. Finally, Ian Willis (Einstein College of Med) will describe recent work about perturbations to RNA polymerase III transcription and the effects on function in the brain, specifically obesity and neurodegenerative disease. Collectively, these talks explore systems that contribute to energy balance, and how they contribute to obesity.

SHORT COURSE • TUESDAY • 4:30 P.M. - 6:30 P.M. • GALLATIN

New and Evolving Imaging Approaches for Evaluating Neural Circuit Activity

Chair: James Otis
Presenters: Megha Sehgal, Jonathan Marvin, Vijay Mohan K. Namboodiri, James Otis

Understanding how complex brain circuits contribute to behavior in health and disease states relies on evaluating the activity of those circuits in awake, behaving animals. New and evolving imaging approaches now allows simultaneous monitoring of activity in hundreds to thousands of cell-type specific neurons in vivo, and such approaches can be combined with both classic and newly-developed experimental techniques to identify how recorded activity functionally relates to behavioral output. Despite the development and improvement of these approaches over the past decade, major hurdles limit the breadth to which we can understand neural circuit activity. Here, we discuss advantages, limitations, and new frontiers for imaging approaches in neuroscience, specifically related to:
(1) Microscopy, led by Dr. Megha Sehgal from University of California Los Angeles (2) Fluorescent sensors, led by Dr. Jonathan Marvin from Janelia Research Campus (3) Data processing and analysis, led by Dr. Vijay Namboodiri from University of Washington (4) Behavioral models, led by Dr. James Otis from Medical University of South Carolina.

PANEL • TUESDAY • 4:30 P.M. - 6:30 P.M. • GIBBON

Of Shape and Function: Microtubule Remodeling in Neurological and Psychiatric Disorders

Chairs: Candice Contet, Amynah Pradhan
Presenters: Annie Andrieux, Eleanor Coffey, Amynah Pradhan, Candice Contet

Mature neurons must maintain their highly asymmetric shape but also remain flexible to adapt their morphology to new functional demands. This dual capacity for stability and plasticity derives largely from the microtubule cytoskeleton, which can be stable or dynamic. Microtubule dynamics is modulated by post-translational modifications of tubulin and by interactions with multiple stabilizing and destabilizing proteins. Proper orchestration of these complex regulatory mechanisms is critical to the activity and plasticity of neuronal circuits, and microtubule dysfunction causes pathological states. Accordingly, microtubules have emerged as a therapeutic target for several neurological and psychiatric disorders. In this panel, Dr. Annie Andrieux (Grenoble Institute of Neuroscience) will discuss how the post-translational modification of tubulin affects microtubule dynamics and control synaptic plasticity and cognitive abilities. Dr. Eleanor Coffey (University of Turku) will

then show how post-translational modifications to microtubule regulatory proteins by c-Jun N-terminal kinase change in different brain regions with behavior and circuit activity related to anxiety, depression and schizophrenia. Dr Amynah Pradhan (University of Illinois at Chicago) will then show that neuronal complexity in key brain regions decreases in animal models of chronic migraine, and that histone deacetylase 6 inhibitors can restore this complexity and inhibit migraine-associated pain and aura. Finally, Dr. Candice Contet (The Scripps Research Institute) will talk about the effect of chronic alcohol exposure on neuronal morphology and tubulin isotype expression in the prefrontal cortex and show that manipulation of microtubule composition or dynamics can alter alcohol drinking in dependent mice. Altogether, these panelists will introduce new data highlighting recent advances in our understanding of the regulatory mechanisms governing microtubule dynamics and their role in brain pathologies.

PANEL • TUESDAY • 4:30 P.M. - 6:30 P.M. • LAKE

A Better Pair of Goggles: Super-Resolution Imaging of Synapses

Chair: Mark Dell'Acqua
Presenters: Daniel Choquet, Matthew Dalva, Katharine Smith, Mark Dell'Acqua

Synapses are the fundamental units of information processing and storage in neuronal circuits. Despite their submicron dimensions, synapses are structurally complex and contain thousands of different proteins that regulate synaptic transmission, including receptors, ion channels, adhesion molecules, scaffolds, and signaling proteins. With the advent of super-resolution fluorescence imaging methods that break the diffraction limit of visible light (~250 nm), such as Stimulated-Emission Depletion (STED), Structured Illumination Microscopy (SIM), Stochastic Optical Reconstruction Microscopy (STORM) and Photoactivation Localization Microscopy (PALM), neuroscientists gained unprecedented abilities to interrogate sub-synaptic structure, organization, dynamics, and function on the nanometer scale, including how postsynaptic receptors are aligned across the synaptic cleft with sites of presynaptic neurotransmitter release. In particular, it is thought that this nanoscale organization of receptors is crucial for tuning synaptic transmission. Daniel Choquet (CNRS U. Bordeaux) will present new results combining super-resolution imaging and electrophysiology to further define the links between the regulation of AMPA receptor nanoscale dynamic organization and excitatory synaptic plasticity. Next, Matthew Dalva (Thomas Jefferson Univ.) will present new results that begin to resolve how the nanoscale organization of excitatory synapses in dendritic spines changes following spine structural plasticity. Katharine Smith (Univ. Colorado) will then present new work characterizing how GABAA receptors and pre- and postsynaptic scaffolds are

organized into sub-synaptic nanodomains at inhibitory synapses and how this changes during plasticity. Finally, Mark Dell'Acqua (Univ. Colorado) will present new findings showing how palmitoylation of the postsynaptic kinase-phosphatase scaffold protein AKAP79/150 regulates its nanodomain targeting and mobility dynamics at excitatory synapses.

PANEL • TUESDAY • 4:30 P.M. - 6:30 P.M. • LAMAR

Why Can't You Hear Me? "Auditory" Circuits in Health and Disease

Chairs: Patrick Kanold, Li Zhang
Presenters: Merri Rosen, Jan Schnupp, Shaowen Bao, Gregg Recanzone

The central auditory system is fundamental for human communication and malfunction of auditory circuits is associated with many diseases. However, malfunction of auditory perception involves many areas outside the canonical auditory system. In this panel, we will discuss the circuits and function of cortical and subcortical auditory processing centers and how their function is impacted or improved by experience, stress, hearing loss, etc. Dr. Patrick Kanold (Univ. Maryland) will discuss how developmental exposure to sound stimuli shapes the circuits of the auditory cortex. Dr. Merri Rosen (NEO MED) will discuss the detrimental effects of early life stress on the auditory system and its interactions with early hearing loss. Dr. Jan Schnupp (City U., Hong Kong) will discuss how the auditory system can adjust to artificial stimulation with cochlear implants (CIs) and how the mature, deaf auditory system can rapidly develop essentially normal binaural sensitivity with CIs despite a lack of hearing experience in early life. Dr. Li Zhang (USC) will discuss a noncanonical central auditory pathway and its function. Dr. Shaowen Bao (U. of Arizona) will discuss how noise-induced hearing loss alters auditory cortical circuits and function. Dr. Gregg Recanzone (UC Davis) will discuss changes in central auditory pathways as a function of aging in primates.

PANEL • TUESDAY • 4:30 P.M. - 6:30 P.M. • TALUS

Dopaminergic Modulation of Learning and Cognition

Chairs: Munir Kutlu, Amy Johnson
Presenters: Munir Kutlu, Daniel Covey, Stephanie Borgland, Joshua Berke

The involvement of dopamine in reward processing and addiction has been well established by a large literature suggesting that dopamine neurons encode reward prediction error. However, recent evidence suggests that dopamine plays a broader role encompassing multiple facets of learning and cognition. Here, our panel will highlight new and exciting research underlying how dopamine encodes information during learning of bimodal reward as well as bimodal

outcomes. First, Dr. Munir Gunes Kutlu will showcase novel research on how nucleus accumbens (NAc) dopamine shapes attentional components of reward and aversive learning. Next, Dr. Daniel Covey will show that mesolimbic dopamine transmission not only drives goal-directed behavior but also encodes the information related to this type of learning. In addition, we will present data showing the effects of upstream and downstream modulators of dopamine on decision making and reinforcement learning. Specifically, Dr. Stephanie Borgland will present data suggesting that lateral hypothalamic orexin and dynoprhin projections onto ventral tegmental area (VTA) dopamine neurons controls reward-seeking behavior and determines reinforcer- and cue-driven behaviors. Finally, Dr. Joshua Berke will present new data from his laboratory investigating how NAc cholinergic interneurons mediate dopamine release during adaptive decision making under distinct cognitive demands of spatial foraging. Overall, our panel will offer a new framework of the multifaceted action of pre- and postsynaptic dopamine in learning and cognition that supersedes dopamine signal as solely encoding the error of predicted outcomes.

Tuesday Evening Panel Sessions

PANEL • TUESDAY • 7:00 P.M. - 8:30 P.M. • AMPHITHEATER

Reacting to the Bumps: Diverse Mechanisms Through Which Different Systems Maintain Homeostasis

Chair: Shane Hentges
Presenters: Zachary Knight, Matt Carter, Stephanie Padilla, Andrew Rau

The body's ability to maintain a relatively stable internal environment is remarkable. From nutrient and fluid sensing to temperature regulation and cyclic regulation of sleep and hormones. The breadth of mechanisms used to achieve homeostasis is notable and the panelists will highlight their latest findings regarding adaptive responses in various homeostatic systems. Zachary Knight (UCSF/HHMI) will share results from his research on neural mechanisms that govern hunger and thirst. He will discuss results from calcium imaging studies demonstrating that key homeostatic neurons receive sensory information from the outside world, which they use predict impending physiologic changes and adjust behavior preemptively. He will discuss how these homeostatic circuits integrate external sensory cues with internal signals arising from the body in order to generate and shape goal-directed behaviors. Matt Carter (Williams College) will discuss his work aimed at understanding the interaction between feeding and sleep circuits. He will share recent work showcasing how feeding-related neurons in the arcuate nucleus affect sleep/wake behavior, as well as new work about how different states of sleep and arousal affect these neurons in freely moving animals. Stephanie Padilla (University of Massachusetts) will discuss her work on the influence of steroid

hormones on thermal regulation. She will present data using functional circuit mapping techniques to define the neurons, circuits and signaling molecules that lead to vasomotor responses in awake behaving mice. Andrew Rau (Colorado State University) will present work highlighting the role of the fast-acting transmitters GABA and glutamate in the regulation of hypothalamic POMC neurons. He will show that POMC neurons receive a significant GABAergic input from the dorsomedial hypothalamus, while glutamatergic inputs largely originate from the VMH. He will then discuss how these inputs affect, and are affected by, food intake.

PANEL • TUESDAY • 7:00 P.M. - 8:30 P.M. • CANYON

Computational Models of Inhibitory Control

Chair: Alain Dagher
Presenters: Michael Frank, Valerie Voon, Frederike Petzschner

Inhibitory control is thought to be an important process in a number of psychiatric and medical conditions, including addiction, obesity, Parkinson's Disease and Pathological Gambling. Recent computational approaches have allowed researchers to model inhibition in a variety of ecologically relevant tasks. Speakers will present new data from healthy participants and individuals with obesity, problem gambling, obsessive-compulsive disorder, and Parkinson's Disease.
Chair, Alain Dagher will briefly introduce the evidence that impaired inhibitory control is a common trait across a variety of neuropsychiatric disorders.
Michael Frank will present computational models on frontal - basal ganglia interactions to support cognitive control over action selection. He will use multiple levels of description, linking neurophysiological signatures of spiking and oscillations to inhibitory control and modulation of decision thresholds.
Valerie Voon will show that intentional inhibition, although poorly understood, represents a highly ecologically valid process underlying daily actions and pathological processes. She will present intracerebral recordings from Parkinson's disease during deep brain stimulation surgery of the subthalamic nucleus. Recordings during voluntary inhibitory control reveal new insights about the role of the subthalamic nucleus in cortico-striatal motor control.
Frederike Petzschner will provide evidence that disorders such as pathological gambling and obsessive-compulsive disorder are centered around a failure of inhibitory control. She will show that impulsive and compulsive tendencies may be dissociated using a novel experimental design in combination with computational models of structure learning in pathological gamblers, recreational gamblers and participants with obsessive-compulsive traits.

Candidate Neuroimaging Biomarkers for Synucleinopathies

Chairs: Daniel Huddleston, Xiaoping P. Hu
Presenters: Xiaoping P. Hu, Daniel Huddleston, Kejal Kantarci

Parkinson's disease (PD) and dementia with Lewy bodies (DLB) are progressive neurodegenerative diseases characterized pathologically by the accumulation of alpha-synuclein aggregates in the brain. They are therefore referred to as synucleinopathies. Emerging MRI and radionuclide imaging markers of symptomatic and prodromal synucleinopathy show promise for clinical and translational applications.

Presenter #1: Xiaoping Hu, PhD, Quantitative Neuromelanin-sensitive MRI

Neuromelanin-sensitive MRI is a technique that has been used to assess neurodegeneration in substantia nigra (SN) and locus coeruleus (LC). This talk will discuss the technique, followed by a review of its applications in the study of SN and LC in synucleinopathy research. Its reproducibility and application in region of interest selection will also be discussed.

Presenter #2: Dan Huddleston, MD, Brainstem MRI Markers of Prodromal and Manifest Synucleinopathy

Neuroimaging markers of brainstem pathology have potential applications for subject selection and as surrogate outcome measures to enhance the success of neuroprotective therapeutics trials for synucleinopathies. Neuroimaging measures sensitive to prodromal neurodegeneration may enable clinical trial designs for therapeutics designed to prevent PD, DLB and multiple system atrophy. This talk will review candidate brainstem MRI markers of neuromelanin, iron and microstructural disease pathology with potential applications in these areas.

Presenter #3: Kejal Kantarci, MD, Radionuclide and MR Imaging Markers of Cortical and Subcortical Pathology in Synucleinopathy

Radionuclide imaging allows in vivo assessment of metabolism and other molecular aspects of neurodegeneration. FDG-PET and arterial spin labeling MRI detect signatures of regional cortical hypoperfusion, and may assist both clinical diagnosis and therapeutic trial design. Dopamine transporter imaging also shows promise for prodromal detection and monitoring of synucleinopathies.

Life Science Entrepreneurship: Should You Take the Slope That Leads to Commercialization?

Chair: Bradley Tanner
Presenters: Bradley Tanner, Jason Eriksen, Susan Tappan

Concept: A Career Development Workshop for neuroscientists who are considering pursuing entrepreneurship and commercialization.
Goal and Experience: The goal is to help life scientists at different points in their career become aware of and able to investigate entrepreneurial career options that utilize their unique talents. This is a planning and discussion workshop requiring active thought, participation, and contribution; this a not a lecture or a set of personal stories. Every entrepreneur carves their own path down the entrepreneurial slope.
Participants can: 1) assess the steepness and challenge of an entrepreneurship slope, 2) determine if going down that slope is something they might want to attempt. Entrepreneurship is NOT the "best" slope for everyone; only the life scientist can make that decision, 3) [if entrepreneurial intent exists], identify the equipment they lack and specific challenges that they will encounter, build their confidence in taking on the challenges, and layout a plan including the potential of grabbing the NIH SBIR flag at the bottom!
We highlight NIH SBIR funding because the bar to obtaining a Phase I SBIR is low compared to angel, VC or Private Equity funding. Scientists are already excellent grant writers and universities and the government have tremendous resources to support an SBIR application.
Presenters: Bradley Tanner, MD, ME is a psychiatrist with a wealth of 25 years of SBIR experience including on SBIR review panels. His company has received multiple SBIR Phase I and Phase II awards stretching back to 1995 and totaling over $20 million. Jason Erikson, Ph.D. is a regular WCBR attendee and Ph.D. neuroscientist who has founded 2 companies [both still active] and is working on a third company seeking SBIR funding. Susan Tappan, Ph.D. is Scientific Director at MBF Bioscience and has a broad interest in developmental neuroscience with a focus in neuroanatomy.

PANEL • TUESDAY • 7:00 P.M. - 8:30 P.M. • GALLATIN

Ventral Striatum Dopamine Encoding of Learning and Motivated Behaviors

Chair: Ryan Farero
Presenters: Matthew Wanat, Ryan Farero, Erin Calipari

Ventral striatum dopamine release is a fundamental neural signal mediating the acquisition and maintenance of reinforced behaviors. Aberrant signaling of dopamine within the ventral striatum is hypothesized to contribute to an array of mental illnesses. As such investigations on the role of dopamine transmission in normal and pathological mental function is important to elucidate potential targets for the development of therapeutic strategies for mental illness. This panel will present studies that examine dopamine transmission within the nucleus accumbens during reinforced behaviors, and how these signals contribute to learning and motivation during rodent behavioral assays. First, Matt Wanat (UTSA) will present data investigating the role of ventral striatal dopamine signaling in changing subjective preference. Next, Ryan Farero (UW) will describe data examining the role nucleus accumbens core dopamine transmission has on addiction-related behaviors during the presentation of drug associated stimuli. Lastly, Erin Calipari (Vanderbilt University) will discuss data using in vivo optical tools to demonstrate the integration of signals within the ventral striatum that encode salience and novelty, during reinforcement controlled by positive and negative stimuli. Together this panel will discuss a range of behavioral assays that examine ventral striatum dopamine encoding of reinforced behaviors in normal and pathological animal models.

PANEL • TUESDAY • 7:00 P.M. - 8:30 P.M. • GIBBON

Regulation of Motivation for Food, Sex and Drugs by Ovarian Hormones

Chairs: Yanaira Alonso-Caraballo, Tracy Fetterly
Presenters: Jill Becker, Annabell Segarra, Yanaira Alonso-Caraballo

Female neurobiology is understudied in biomedical research. Consequently, critical gaps remain in our understanding of the mechanism of how ovarian hormones and the reproductive cycle regulate motivated behaviors, reward learning, and corresponding plasticity. Cyclic changes in ovarian hormones potently regulate brain circuits for motivation to pursue sex, and they are key regulators of motivation for food cues and drugs of abuse. This panel will discuss our latest understanding of the mechanistic underpinning of how the estrous cycle and ovarian hormones modulate reward and motivation in mesocorticolimbic brain circuits. First, Dr. Jill Becker (University of Michigan), will present new data on the interaction between estradiol, estradiol receptors

and dopamine transmission that regulate motivational competition for sex or food. Next, Dr. Annabell Segarra (University of Puerto Rico) will describe studies on how age and sex shape estradiol-induced neuroplasticity. Finally, Yanaira Alonso-Caraballo (University of Michigan) will describe changes in the excitability of medium spiny neurons in the nucleus accumbens during different phases of the estrous cycle and how they relate to changes in processing of food-cues in rat models of obesity. Tracy Fetterly will provide introductory comments and lead discussion of the presentations. Together this panel will summarize our latest understanding of brain mechanisms for how the estrous cycle and ovarian hormones shape motivational arousal, and flexible decision making.

PANEL • TUESDAY • 7:00 P.M. - 8:30 P.M. • LAKE

Epileptology: From Basic Science to Applied Bioengineering

Chair: Olaf Paulson
Presenters: Claude Wasterlain, Lars H. Pinborg, Sándor Beniczky

Olaf Paulson will provide introductory comments and lead the discussion of the presentations.
This session will highlight exciting recent advances in epileptology, from basic science and understanding of epileptogenesis, to automated seizure detection and characterization using wearable devices.
Claude Wasterlain: Epileptogenesis: In Search of the Holy Grail
Finding an antiepileptogenic treatment remains the Holy Grail of epilepsy. We will review current evidence about the basic mechanisms of epileptogenesis, the nature of the latent period and the hippocampal networks involved in animal models of acquired focal epilepsy. We will review the filter hypothesis, which postulate that hippocampal lesions compromise neural networks which prevent excessive build-up of excitation and seizures.
Lars H. Pinborg: The Cognitive, Behavioral and Psychiatric Comorbidities of Epilepsy: How Can We Improve?
It is increasingly recognized that the burden of epilepsy is more than just seizures. In particular, depression has been demonstrated to be more predictive for patient's quality of life than seizures. Cognitive and behavioral problems are related to poor psychosocial outcome and stigmatization. Is it possible to identify patients at special risk of developing comorbidities and initiate preventive strategies so early in the disease process that the outcome of epilepsy improves significantly? Review of the literature and possible future directions are discussed.
Sándor Beniczky: Automated Seizure Detection and Characterization Using Wearable Devices

This presentation will review the published evidence for the accuracy of automated seizure detection and risk assessment of epileptic seizures, and it will highlight future developments in this field.

PANEL • TUESDAY • 7:00 P.M. - 8:30 P.M. • LAMAR

Autism Spectrum Disorder: Mechanisms and Potential Treatments

Chairs: Hsiao-Huei Chen, Brigitta Gundersen
Presenters: Brigitta Gundersen, Hui-Chen Lu, Hsiao-Huei Chen, Evdokia Anagnostou

Autism Spectrum Disorders (ASD) are incredibly heterogenous, differing in symptoms, trajectories, and underlying etiologies. Brigitta Gundersen (Simons Foundation) will introduce the panel and summarize the current status of research from the SPARK Consortium and other cohorts that highlight ASD risk genes, raising key questions and challenges for ASD treatment. The next 3 presentations discuss novel targets for therapeutic intervention in ASD, from growth factors to a phosphatase affecting synaptic function, E:I balance and neural circuits and new clinical trials targeting these mechanisms.
Hui-Chen Lu (University of Indiana) will share her findings that focus on how glutamate transmission affects dendritic patterning through the activity of fibroblast growth factors (FGFs)/FGF receptors (FGFRs) as a possible treatment approach for autism and stress-related psychiatric disorders.
Hsiao-Huei Chen (Ottawa Hospital Research Institute) will present new evidence that protein tyrosine phosphatase PTP1B activity in parvalbumin interneurons affects E:I balances and causes homeostatic maladaptation of inhibitory circuits to impede information processing at the anterior cingulate cortex associated with autism-like behaviors in mice. PTP1B is a phosphatase that disrupts FGFR signaling and accounts for insulin resistance in metabolic syndrome, often encountered in ASD subjects.
Evdokia Anagnostou (University of Toronto) will share her work from a large Canadian cohort of neurodevelopmental disorders and focus on unpublished data from new clinical trials targeting E:I balance and synaptic plasticity. Challenges in cross species translation in this space will be discussed.

WEDNESDAY, JANUARY 29, 2020

Wednesday Morning Panel Sessions

PANEL • WEDNESDAY • 7:30 A.M. - 9:30 A.M. • AMPHITHEATER

Synaptic Mechanisms Underlying the Pathophysiology of Autism Spectrum Disorders

Chair: Katherine Roche

Presenters: Katherine Roche, Helen Bateup, Anis Contractor, Gavin Rumbaugh

Autism Spectrum Disorders (ASDs) are a group of prevalent neurodevelopmental disorders that are characterized by problems with social engagement and communication, inappropriate repetitive actions, perseverative behaviors, and a range of associated symptoms, including sensory and motor abnormalities, intellectual disability, and mood disorders. This panel will bring together neuroscientists with expertise in studying synapse biology to present their findings of how synaptic mechanisms contribute to different molecular, synaptic and circuit phenotypes in models of ASDs. Katherine Roche will describe work from her lab on rare genetic variants in NMDA receptor subunits and in neuroligins that are thought to be pathogenic in some cases of intellectual disability (ID) and ASD. Helen Bateup will present data that explore the neural basis of ASD traits such as behavioral inflexibility, and restricted, repetitive patterns of behavior. In particular, she will discuss work showing that synaptic alterations in the dorsal striatum increase the propensity for motor habit formation, while impaired dopamine signaling results in inflexible decision-making strategies. Anis Contractor will discuss how disruptions in GABAergic signaling during early critical periods affect circuit development and function in mouse models of autism. In particular he will present work in a mouse model of Fragile X Syndrome, a neurodevelopmental disorder that causes intellectual disability and is the largest known cause of autism. Gavin Rumbaugh will discuss work from his lab on how the ASD risk factor, Syngap1, disrupts both synaptic function and intrinsic excitability in developing cortical neurons that contribute to sensory processing.

The Point of Snow Return: Long-Term Effects of Adolescent Cannabinoid Exposure on Drug Addiction and Maladaptive Decision Making in Adulthood

Chairs: Jennifer Wenzel, Natalie Zlebnik
Presenters: Jacqueline-Marie Ferland, Natalie Zlebnik, Jibran Khokhar, Christie Fowler

Cannabinoids (CBs) are the most commonly abused drugs among adolescents, and excessive CB use in this population is associated with the development of psychiatric conditions, including substance use disorder (SUD). However, how CB exposure alters brain function to predispose an individual to SUD remains unclear. This panel will highlight research on the long-term behavioral and neurobiological effects of adolescent CB exposure, including how CB exposure affects self-administration of several different drugs of abuse in adulthood. Dr. Ferland will present recent work exploring the dose-dependent effects of adolescent exposure to the CB delta-9-tetrahydrocannabinol (THC) on cost/benefit decision making, stress reactivity, reward sensitivity, cognition, and impulsivity in adult rats, along with correlated THC-induced neuromolecular changes. Dr. Zlebnik will discuss how CB exposure in adolescence disrupts the development of dopamine neurocircuitry and alters cocaine self-administration, cocaine-mediated anxiety, and cocaine-evoked phasic DA release in adult mice. Dr. Khokhar will present findings from behavioral and electrophysiological studies assessing the impact of adolescent THC vapor exposure, either alone or in combination with alcohol, on instrumental and Pavlovian learning, object recognition memory, delay discounting, alcohol drinking, and corticostriatal function in adult rats. Dr. Fowler will discuss recent studies demonstrating long-term dose- and sex-dependent effects of adolescent nicotine and CB exposure on nicotine self-administration and relapse-related behaviors, as well as how mice respond to acute re-exposure to CBs on nicotine intake in adulthood. Altogether, these presentations provide an overview of our current knowledge on the lasting effects of CB exposure on developing brain function and behavior in rodent models, and they may help to identify mechanisms that may render individuals more susceptible to the reinforcing effects of abused drugs.

PANEL • WEDNESDAY • 7:30 A.M. - 9:30 A.M. • CHEYENNE

Transgenerational Inheritance of Stress and Drug Exposure: Effects on Brain, Behavior, and the Epigenome

Chair: Lisa Goldberg
Presenters: Lisa Goldberg, Julie Blendy, Gregg Homanics, Chris Pierce

Paternal exposure to drugs of abuse or stress can produce profound effects on the physiology and behavior of offspring via epigenetic modifications. Dr. Goldberg will present on the effect of paternal nicotine exposure on fear conditioning, hippocampal cholinergic functioning, hippocampal gene expression and methylation. The findings in collaboration with Dr. Tom Gould indicate that paternal nicotine exposure resulted in increased fear learning, decreased cholinergic function, and altered gene expression in progeny, producing a phenotype similar to symptoms associated with post-traumatic stress disorder. Dr. Blendy will present her findings regarding the transgenerational inheritance of paternal stress exposure, and its interaction with nicotine exposure. Paternal stress exposure produced a protective phenotype in a sex-specific manner. In the male lineage, grandparent nicotine exposure abrogated nicotine locomotor sensitization in male and transiently enhanced nicotine locomotor sensitization in female grandoffspring. Dr. Homanics will present his work in a rodent paternal preconception chronic intermittent ethanol exposure paradigm, where they have discovered that male offspring of ethanol exposed sires have altered sensitivity to several behavioral effects of ethanol and stress hyporesponsitivity. Mechanistic studies have revealed that ethanol exposure alters the small noncoding RNA content of sperm, possibly via RNA transfer from exosomes to sperm. Dr. Pierce will present his findings that paternal cocaine self-administration hypomethylates sperm Cdnk1a resulting in a selective increase in the expression of this gene in the nucleus accumbens of male offspring, which produces blunted cocaine reinforcement. Together, this panel provides a framework for the behavioral and neurobiological consequences of paternal drug and stress exposure and offer insights into the mechanisms of multigenerational epigenetic inheritance.

PANEL • WEDNESDAY • 7:30 A.M. - 9:30 A.M. • DUNRAVEN/OBSIDIAN

Neuroimaging Applications for Social and Affective Modulation of Pain

Chair: Vitaly Napadow
Presenters: Vitaly Napadow, Patrick Finan, Robert Edwards

Pain perception is more than nociception. The experience of pain is highly modifiable by cortical circuitries which can regulate descending inhibitory and facilitory pathways in the brainstem, as well as sensory, affective, and

cognitive processing in the brain. Hence, social contexts and affective states can significantly contribute to the pain experience, providing pathways for potential therapies to combat chronic pain. In this panel, we will explore cutting edge human neuroimaging approaches to better understand how social and affective determinants can modulate pain perception. Presentations will cover the patient-clinician relationship, which can powerfully shape pain and placebo responses; the neural basis for positive emotional pain inhibition; and the role of catastrophizing in neural response to pain. Dr. Napadow will show that simultaneously recorded (hyperscan) functional MRI in patient-clinician dyads reveals concordant activation of social mirroring, empathy, and theory-of-mind circuitries that support therapeutic alliance within the patient-clinician relationship. Dr. Finan will show that interventions designed to evoke positive emotions, such as listening to individually tailored music when pain is high, alter the functional connectivity of corticostriatal circuits reflecting attentional preference for rewarding over aversive experience. Dr. Edwards will explore pain catastrophizing, a much-studied mindset which incorporates rumination, helplessness, and magnification of the threat value of pain and is well known to upregulate the pain experience. He will discuss recent neuroimaging approaches exploring the cortical circuitries supporting pain catastrophizing in chronic pain patients.

PANEL • WEDNESDAY • 7:30 A.M. - 9:30 A.M. • GALLATIN

The Spectrum of Social Behavior and its Underlying Mechanisms

Chair: Marco Venniro

Presenters: Marco Venniro, Marijke Achterberg, Alexa Veenema, Sam Golden

Social interaction is an ethologically complex behavior with a spectrum ranging from social play to aggression. Both forms of interaction can be rewarding for either humans or laboratory animals. Lately, these behaviors have increasingly been modeled and incorporated in preclinical animal models to study underlying neural mechanisms. Based on this, we will present recent findings exploring the behavioral and neurobiological features of the large spectrum of social interactions. Marco Venniro (NIDA) will discuss data from a novel community reinforcement approach rat model, showing the critical role of central amygdala PKCδ-expressing neurons in inhibition of incubation of methamphetamine craving after social choice-induced voluntary abstinence. Marijke Achterberg (Utrecht University) will give an overview of the neuropharmacology of social play and will show data on individual differences in social play and how these differences affect adult behavior. Alexa H. Veenema (Michigan State University) will show data on the role of oxytocin in bed nucleus of the stria terminalis and in the nucleus accumbens in facilitating social recognition and social play behavior in sex-specific ways, respectively.

Sam Golden (University of Washington) will present a model of compulsive aggression seeking and relapse and the role of specific cell-types in controlling aggression reward. He will also highlight recent advances in computer vision and machine learning for automated scoring of aggressive behavior. Collectively, this panel will illustrate the current and future directions of the neuroscience of social behaviors.

PANEL • WEDNESDAY • 7:30 A.M. - 9:30 A.M. • GIBBON

Inflammation as a Risk Factor for Psychiatric Illness

Chair: Victoria Risbrough
Presenters: Samantha Friend, Lilly Schwieler, Sophie Erhardt, Margarita Behrens

Converging evidence implicates inflammation as a risk factor for psychiatric illnesses. Inflammatory factors may serve as biomarkers of illness risk and inform treatment strategies. This symposium will provide new insights on both central and peripheral immune contributions to mental illness. We will discuss clinical and animal data on inflammatory risk factors, their biochemical consequences, and potential mechanisms for the effects of inflammation on psychiatric risk. Dr. Friend will discuss the role of immune signaling in posttraumatic stress disorder (PTSD) and present new preclinical studies using genetic and viral tools dissecting the role of C-Reactive Protein and Interleukin-10 in rodent models of PTSD. She will also discuss the potential for neuronal- and astrocyte-derived exosomes to probe CNS inflammation in trauma disorders. Dr. Schwieler will discuss the significance of G protein receptor kinase (GRK)-3 for the induction of psychosis and cognitive dysfunctions. Recent studies suggest that the GRK3 receptor controls p2x7-induced secretion of the pro-inflammatory cytokine interleukin (IL)-1β. In this presentation, Dr. Schwieler will present new data showing that mice with a targeted deletion of GRK3 display increased hippocampal levels of IL-1β and induced activity in the kynurenine pathway along with increased synthesis of kynurenic acid and enhanced dopamine-response as well as aberrant behavior, such as disrupted prepulse inhibition. Dr. Erhardt will discuss the role of central and peripheral activity in the kynurenine pathway on suicide risk and bipolar disorder. This pathway, which is activated by inflammation, may constitute a causative link between inflammation and psychiatric symptoms, due to its production of metabolites acting on NMDA receptors. Dr. Behrens will present data on the long term effects of disruption of the maternal immune environment on DNA methylation patterns and development of cortical pyramidal neurons.

PANEL • WEDNESDAY • 7:30 A.M. - 9:30 A.M. • LAKE

Behavioral Correlates of Circuit and Metabolic Dysfunction in Various Models of Traumatic Brain Injury: Finding Common Ground

Chair: Akiva Cohen
Presenters: Kaitlin Best, Amber Nolan, Akiva Cohen, Edward Hall

Annually 1.5 million Americans sustain a traumatic brain injury (TBI) from which 230,000 people are hospitalized and survive, and 50,000 people die. Assorted traumas cause TBI, including acceleration and impact. Ensuing pathologies are linked to a range of clinical severities. Though numerous studies have revealed TBI-induced alterations in cellular, synaptic and metabolic function in frontolimbic circuits, core pathologies shared across injury models and severities and their relevance to neurobehavioral prognosis have yet to be definitively determined. Our panel will compare and contrast maladaptive neural remodeling and related behavioral deficits observed in multiple models. Kaitlin Best (CHOP/UPENN) will present findings from a lateral fluid percussion injury (LFPI) model on the effect of mild TBI on pain sensitivity and pain-related aversive behaviors, as linked to basolateral amygdala function. Amber Nolan (UCSF) will present a model of frontal lobe contusion that produces deficits in reversal learning and alterations in inhibitory circuits in the orbitofrontal cortex. Akiva Cohen (CHOP/UPENN) will discuss impairments in a working memory task after mild LFPI and underlying alterations in ventral hippocampal-medial prefrontal cortex circuit function. Edward Hall (UKy) will show data on the combination of mechanistically complementary antioxidant agents to mitigate mitochondrial dysfunction, decrease cortical lesion volume and improve motor and memory function after moderately severe focal (CCI) brain injury. This session will couple two seasoned investigators together with two young investigators new to a WCBR panel to inform the neuroscience community on the complexity of physiological, biochemical and behavioral changes observed after TBI. The panel will form a foundation to discuss the challenges and opportunities to develop therapies for a heterogenous injury phenotype with a focus on translational mechanisms to improve human outcomes after brain injury.

PANEL • WEDNESDAY • 7:30 A.M. - 9:30 A.M. • LAMAR

Navigating the Biology of Schizophrenia: From Genetic Risk to Novel Treatment Targets

Chair: Thomas Hyde
Presenters: Brady Maher, Thomas Hyde, Elizabeth Tunbridge, Robert Sweet

As Genome Wide Association Studies generated by the Psychiatric Genetics Consortium have accrued increasingly larger numbers of subjects, the number of loci associated with significant risk of schizophrenia have correspondingly increased. Understanding the mechanisms of genetic risk are the first steps towards understanding the pathobiology of complex behavioral disorders. The development of novel medications with greater efficacy and fewer side effects are dependent upon clarity in the mechanisms of risk. In order to translate clinical genetics into mechanisms of risk, a multiplicity of approaches are being employed. Brady Maher will present the results of investigations using human induced pluripotent stem cells differentiated into cortical neurons to assess molecular and functional changes associated with schizophrenia-derived polygenic risk scores. Thomas Hyde will present data from postmortem human brain studies of dentate gyrus on regionally specific signatures of gene expression associated with specific genetic risk loci in schizophrenia. Elizabeth Tunbridge will present findings from in depth analyses of CACNA1C, a gene that is well established as part of the risk architecture of schizophrenia, and also a tantalizing potential therapeutic target. Finally, Robert Sweet will focus on a molecular point of convergence, the phosphorylation of Microtubule-associated Protein 2 (MAP2), which is downstream of multiple genes now established by unbiased methods as schizophrenia risk genes. MAP2 phosphorylation is substantially altered in schizophrenia and associates with dendritic and proteomic pathology. This panel will demonstrate the utility of a diversity of approaches in pursuit of a greater understanding of the pathobiology of schizophrenia, and the promise of these approaches in identifying new targets for treatment.

PANEL • WEDNESDAY • 7:30 A.M. - 9:30 A.M. • TALUS

Dopamine in Reward and Learning

Chair: David Bortz
Presenters: Briac Halbout, Elizabeth Holly, David Bortz, Kenneth Amaya

The ability to learn to obtain rewards and to adapt such behaviors in the face of a changing environment is critical for survival and dopamine (DA) is strongly implicated in these processes. This panel will discuss recent findings describing the ways in which DA signaling can affect reward learning in goal directed and pavlovian learning, as well as cognitive flexibility.

Briac Halbout will describe recent work investigating the contribution of the mesocorticolimbic system in coordinating discrete reward-seeking and reward-retrieval behaviors in rats. Dr. Halbout will discuss how reward-paired cues and expected reward value influence the performance of reward-seeking and -retrieval responses.
Elizabeth Holly: The dorsomedial striatum (DMS) is a key mediator of goal-directed (operant) behavior, serving as a critical node integrating sensorimotor, motivational, and cognitive information to drive motor execution. I will describe how DMS DA signaling evolves during the acquisition of an operant task, and how these signals can be locally modulated by striatal interneurons to accelerate learning.
David Bortz: DA release is necessary for cognitive flexibility tasks. However, little is known about how circuitry upstream of the midbrain, which regulates DA release via control of population activity, could affect strategy switching. My results suggest that activation of the medial septum enhances reversal learning and set shifting performance via a unique, bidirectional regulation of DA neuron population activity.
Kenneth Amaya: Appetitive sign-tracking (ST) is a phenomenon involving the development of a conditioned response to cues that are predictive of reward in Pavlovian conditioning. Recent reports have indicated that ST is resistant to nausea-induced outcome devaluation. My present findings suggest that (1) sign-tracking behavior is, in fact, sensitive to outcome devaluation and (2) residual sign-tracking behavior does not require nigrostriatal projections.

Wednesday Afternoon Panel Sessions

PANEL • WEDNESDAY • 4:30 P.M. - 6:30 P.M. • AMPHITHEATER

The Interaction Between Diet and Cognitive Flexibility

Chairs: Laura Corbit, Stephanie Borgland
Presenters: Laura Corbit, Stephanie Borgland, Amy Reichelt, Alain Dagher

Obesity has reached alarming prevalence worldwide. Although many people attempt to control their weight, most fail over the long-term indicating lack of flexible control. This session will focus on recent research exploring the relationship between diet and cognitive flexibility. Dr. Corbit will describe how an obesogenic diet reduces sensitivity to outcome value, dysregulates glutamate transmission in corticostriatal circuits, and how restoring glutamate homeostasis in the striatum can improve behavioural performance. The orbitofrontal cortex (OFC) receives sensory information about food and integrates this with expected outcomes. Dr. Borgland will present data demonstrating that exposure to a palatable diet alters astrocyte modulation of glutamate homeostasis within the OFC, which influences GABAergic neurotransmission. She will also present data showing impaired reward

devaluation in obese rodents and restoration by increasing OFC GABAergic transmission. In addition to effects on projection neurons, obesity is increasingly recognized to alter plasticity through effects on extracellular matrix components called perineuronal nets-structures that encase parvalbumin interneurons. Dr. Reichelt will describe how modulation of parvalbumin neuron activity with DREADDs affects memory performance in both control and obese mice. Finally, Dr. Dagher extends the study of the relationship between diet and cognition to humans. He will discuss work analyzing cognitive performance, personality, and MRI derived cortical thickness and connectivity patterns related to BMI. This data shows patterns of reduced cognitive flexibility and impulsivity related to higher body weight as well as data suggesting that the genetic factors that confer vulnerability to obesity are mostly expressed in the brain, and likely relate to higher cognitive functions such as flexibility and self-regulation. In sum, this session will provide insight into the complex interplay between diet and cognition.

PANEL • WEDNESDAY • 4:30 P.M. - 6:30 P.M. • CANYON

AMPA Receptors in Synaptic Plasticity: From Biogenesis to Potentiation

Chair: Ulli Bayer
Presenters: Ingo Greger, Bernd Fakler, Elva Diaz, Ulli Bayer

Higher brain functions such as learning, memory and cognition are thought to require the ability of synapses to undergo plastic changes in their strength. At excitatory synapses, these changes are thought to be largely expressed by changes in the AMPA-type glutamate receptors (AMPARs). This panel will discuss recent advances in our understanding of AMPAR structure and regulation. The panel will start out with detailed discussion of AMPAR structure and biogenesis, and then move towards the signaling mechanisms that regulate AMPAR function at the synapse. Ingo Greger (MRC Laboratory of Molecular Biology, UK) will present cryo-EM structural and functional experiments elucidating the role of TARP auxiliary subunits in AMPA receptor synaptic transmission and plasticity. Implications for function and regulation will be discussed. Bernd Fakler (University of Freiburg, Germany) will describe analysis of the AMPAR interactome and how specific protein complexes regulate the biogenesis, transport, and function of the receptor. Elva Diaz (University of California, Davis) will describe the regulation of excitatory synapse plasticity and of cognitive function by the AMPAR-associated protein SynDIG4. Ulli Bayer (University of Colorado Anschutz Medical Campus) will describe the bi-directional regulation of AMPAR-dependent synaptic strength by CaMKII, including a novel mechanism that directs the differential response to the stimulation frequency.

PANEL • WEDNESDAY • 4:30 P.M. - 6:30 P.M. • CHEYENNE

Cells & Circuits Contributing to Opioid Use Disorder

Chairs: Alexander Smith, Michael Stefanik
Presenters: Michael Stefanik, Giuseppe Giannotti, Emmanuel Darcq, Alexander Smith

The U.S. is currently in the midst of an opioid overdose epidemic that claims more than 115 lives each day. Opioid dependence is characterized by vulnerability to relapse following protracted abstinence, and relapse prevention is a primary outcome goal of efforts for novel pharmacotherapeutic development. All currently approved FDA-approved therapeutics for opioid use disorder directly target opioid receptors, and thus may serve as replacement therapies, not necessarily addressing the root cause of the disorder. In this panel, we will discuss our efforts on understanding the neurobiology critical for opioid withdrawal and relapse, with a focus on potential for development of circuit–based therapeutics for prevention of opioid use disorder. First, Michael Stefanik (North Central College) will present data demonstrating maladaptive AMPA receptor plasticity in the nucleus accumbens (NAc) that is produced by extended-access oxycodone self-administration, and underlies incubation of craving following prolonged abstinence. Next, Giuseppe Giannotti (UC Denver, Anschutz Medical Campus) will present data optogenetically dissecting the role of the paraventricular thalamic projections to NAc in mediating opioid aversion, withdrawal, and reinstatement of heroin seeking. Emmanuel Darcq (McGill University) will then talk about whole brain functional connectivity in a mouse model of protracted abstinence from chronic morphine, with a focus on relation to despair behavior. Finally, Alexander Smith (Icahn School of Medicine at Mount Sinai) will present translational data on development of a novel Orexin receptor 1 specific antagonist, and its efficacy in reducing opioid self-administration, craving, and reinstatement. Together, this session will highlight recent advances in our understanding of neurobiology of opioid addiction, and how this may be targeted for development of novel circuit-based pharmacotherapeutics.

PANEL • WEDNESDAY • 4:30 P.M. - 6:30 P.M. • DUNRAVEN/OBSIDIAN

Some Will Ski Down the 'Dark Side': Uncovering Neural Substrates of Individual Vulnerability to Mood and Anxiety Disorders

Chair: Marek Schwendt
Presenters: Marek Schwendt, Lori Knackstedt, Jennifer Rainville, Eric Nunes

Pre-existing biological factors contribute to individual vulnerability to develop stress-induced anxiety and mood disorders. This panel will highlight recent findings on neurobiological mechanisms of vulnerability/resilience.

Marek Schwendt will present data indicating a critical role for BLA mGlu5 receptors in resilience to long term anxiety after predator scent stress in male rats. He will provide evidence that upregulation of mGlu5 in this brain region predicts phenotypic stress resilience, while inhibition of this receptor population exaggerates contextual fear. Next, Lori Knackstedt will discuss sex differences in anxiety behaviors in a rodent model of PTSD. She will present data demonstrating that male and female rats display distinct fear and anxiety symptoms that persist weeks after a single predator scent exposure. Potential sex differences in mGlu5 mRNA expression in the amygdala-PFC circuit will also be discussed. Jennifer Rainville will introduce research showing that women and men with treatment resistant depression display unique cytokine profiles when compared to controls or treatment-responsive patients. She will show how backtranslation of these sex differences into mice reveals that activation of pro-inflammatory cytokines are sex and depression/stress-type specific. She will also examine the correlation between specific behaviors and symptoms with individual cytokine concentrations to identify potential targets for susceptibility and resilience in males and females. Eric Nunes will introduce the role of phasic dopamine (DA) activity and release in the VTA to NAc pathway in stress and depression-related behavior in rodents. He will discuss how VTA cholinergic receptors, which regulate phasic DA release in the NAc, also mediate behavioral responses to stress and anxiety in animal models. Specifically, he will show data supporting the hypothesis that M5 blockade in the VTA attenuates anhedonic, anxiogenic and depressive-like responses in rat models.

PANEL • WEDNESDAY • 4:30 P.M. - 6:30 P.M. • GALLATIN

Reward Under a Bad Sign: Neural Mechanisms to Navigate Motivated Action Under Risky Conditions

Chair: Michael Saddoris

Presenters: Catilin Orsini, Michael McDannald, David Jacobs, Michael Saddoris

In natural settings, animals are tasked with continuously making decisions that simultaneously weight the prospective gains available (such as food or mates) while minimizing risk factors like predation or injury. Because risk and reward probabilities are uncertain in these settings, animals must decide the conditions under which to seek valuable outcomes under threat. Thus, conflict between motivated behavior under stochastic risk likely depends on neural circuits that are able to detect and resolve these conflicts in order to optimally guide behavior. This symposium will review innovative models of rodent models of these risk/reward conflicts, providing new insights into motivation, decision making, punishment and drug dependence. Dr. Caitlin Orsini will discuss the relationship between food seeking in the face of possible punishment and drug-seeking behavior and its underlying neurobiological substrates. Dr.

Michael McDannald will examine how threatening cues exert powerful control over reward, and that ventral pallidum neurons show distinct but overlapping signals for relative threat and reward critical for these processes. David Jacobs from Dr. Bita Moghaddam's lab will present new findings on the potential role of prefrontal cortical regions (mPFC and OFC) in a chained probabilistic punishment resistance task in order to assesses how reward motivated action becomes increasingly resistant to punishment in male and female rats. Finally, Dr. Michael Saddoris will examine how neural pathways in the prefrontal cortex, nucleus accumbens and dorsal striatum distinctly contribute to flexible strategies in continuously risk-updating rodent gambling task. Together, the panel will provide new perspectives on the neural circuits of emergent decision networks that may mediate reward/threat conflict.

PANEL • WEDNESDAY • 4:30 P.M. - 6:30 P.M. • GIBBON

Sex-Differences in Chronic Pain State From the Bench to the Bedside

Chairs: Josee Guindon, Sybil Stacpoole
Presenters: Khalid Benamar, Josee Guindon, Sybil Stacpoole, Vani Selvan

The societal and economic impact of chronic pain is tremendous, accounting for an estimated $600 billion annually in medical expenses and loss of work productivity (Gaskin and Richard, 2012). Despite improvement in our understanding of pain pathways through breakthrough discoveries and use of translational animal pain models, the scourge of the affliction for chronic pain patients continues unabated. The current pharmacological approaches to alleviate pain such as nonsteroidal anti-inflammatory drugs, opioids, anticonvulsants, antidepressants and cannabinoids offer partial and unsatisfactory relief. In this symposium, we will bridge preclinical and clinical studies in regards to chronic pain state related to HIV, chemotherapy, multiple sclerosis and other unknown etiology. Dr. Benamar will discuss chronic pain in preclinical studies in HIV-mouse model and sex-specific findings in analgesic treatments following administration of cannabinoids and anticonvulsants. Dr. Guindon will emphasize on sex-differences found in analgesic effects of antidepressants, anticonvulsants and cannabinoids. She will present new exciting data on the role of sex hormones using her optimized chemotherapy-induced pain model. Dr. Stacpoole, as a physician expert in chemotherapy-induced pain and multiple sclerosis in patients, will share her findings about clinical outcomes and sex-specific differences in treatment options. To conclude our symposium, Dr. Selvan will share her 25 years of clinical expertise in patients care in regards to chronic pain in male and female non-cancer, multiple sclerosis and HIV patients using narcotic (opioids) and non-narcotic therapies such as antidepressants and anticonvulsants. This symposium will shed the

lights on the importance of sex-differences in the treatment of chronic pain and how new preclinical and clinical studies need to take into considerations the role of sex-hormones in the treatment of chronic pain in patients.

PANEL • WEDNESDAY • 4:30 P.M. - 6:30 P.M. • LAKE

Autism Spectrum Disorder - Bedside to Bench

Chair: Angus Wilfong
Presenters: Angus Wilfong, Anne Anderson, Heather Born, Richard Frye

This panel discussion will review emerging basic and translational science that has been driven by the vexing clinical challenge of helping children with autism spectrum disorder and associated comorbidities, particularly epilepsy. These unmet clinical needs provide research challenges and opportunities in the laboratory.

Angus Wilfong (Barrow Neurological Institute) will begin with a clinical case of autism and epilepsy who underwent brain surgery that dramatically resolved both conditions. Anne Anderson (Baylor College of Medicine) will discuss two rodent models of epilepsy (Angelman and tuberous sclerosis) that display features of autism. Heather Born (Baylor) will characterize the social behavioral deficits seen in these models. Richard Frye (BNI) will review his basic science work in how mitochondrial dysfunction may underlie features of autism and epilepsy and how the ketogenic diet is helpful for both conditions.

This session is designed to be interactive, with brief presentations and an extensive discussion period. Registered audience participants will be allowed three minutes and a single slide during the discussion.

PANEL • WEDNESDAY • 4:30 P.M. - 6:30 P.M. • LAMAR

There is an Aptamer for That! Nucleic Acid-Based Chemosensors for Brain Research

Chair: Tod Kippin
Presenters: Kevin Plaxco, Netz Arroyo, Philip Vieira, Karen Scida

Brain function involves myriad interacting chemicals that undergo rapid concentration fluctuations. Current neurochemistry techniques are challenged to appropriately monitor brain chemistry in a number of ways. The focus of this panel is on the electrochemical aptamer-based biosensor (EAB) platform that is capable of versatile measurements of a wide variety of molecules while also providing both high temporal resolution and real-time measurements. In brief, the EAB platform employs electrode surfaces modified with DNA aptamers that are attached to a redox reporter which together allow concentration-sensitive changes in current under voltametric interrogation. Kevin Plaxco (University of California, Santa Barbara) will describe the invention of

the EAB sensors as a generalizable tool for achieving continuous real-time monitoring of a variety of analytes, including neurotransmitters, hormones, and drugs. Next, Netz Arroyo (John Hopkins Medical School) will describe strategies for adopting EAB sensors for measurements in vein and in brain of living subjects with a focus on techniques for probe implantation, drift correction and prevention of probe degradation. Philip Vieira (California State University-Dominguez Hills) will describe the application of EAB sensors for ultra-high precision pharmacokinetic measurements with a focus on individual differences as well as integration of EAB sensors into closed-loop engineering approaches to achieve feedback-controlled drug delivery. Lastly, Karen Scida (Diagnostic Biochips Inc) will discuss incorporation of EAB sensors into electrophysiological platforms in order to achieve simultaneous electrical and chemical measurements of brain activity. Overall, the panel will seek to illustrate the potential of the EAB sensors to advance of our view into brain function as well as provide translational tools to improve management of clinical conditions.

PANEL • WEDNESDAY • 4:30 P.M. - 6:30 P.M. • TALUS

Adapting to Change: The Circuitry Underlying Behavioral Flexibility

Chairs: David Bortz, Anna Radke
Presenters: Anna Radke, David Bortz, Alicia Izquierdo, Zackary Cope

Cognitive flexibility is the ability to shift perspectives and strategies in the face of changing environmental contingencies, a construct that is key to living an independent life. Unfortunately, deficits in cognitive flexibility are among the most pervasive symptoms across psychiatric and neurological disorders. As such, understanding the circuitry that regulates this cognitive construct is a major priority in the field of neuroscience and the topic of this panel. Using fast-scan cyclic voltammetry, Dr. Anna Radke will present data demonstrating a role for dopamine (DA) release in the nucleus accumbens core in reversal learning. She found that manipulation of DA neurons specifically influences perseverative responding during early reversal. Dr. David Bortz will present data showing a key role for the medial septum (MS), via a direct projection to the hippocampus, for both reversal learning and set shifting. His results suggest that activation of the MS enhances reversal learning and set shifting performance via a unique, bidirectional regulation of midbrain DA neurons. Dr. Alicia Izquierdo will present data comparing orbitofrontal cortex (OFC) and anterior cingulate (ACC), together with basolateral amygdala, in flexible reinforcement learning under uncertainty. Her results suggest highly overlapping, less specialized, roles for ACC and OFC in learning under uncertainty that point toward a shared role of both structures in keeping track of outcomes over time. Dr. Zackary Cope will present data examining a role for locus coeruleus inputs to prelimbic/

infralimbic cortex in set shifting. He finds a facilitation of performance on extradimensional shifts following direct activation of this pathway, which results from more consistent performance of new behaviors during the transition between old and new rules. Together, these speakers will provide an up-to-date overview of the breadth of different, but interconnected, neural circuits controlling flexible behavior.

THURSDAY, JANUARY 30, 2020

Thursday Morning Panel Sessions

PANEL • THURSDAY • 7:30 A.M. - 9:30 A.M. • AMPHITHEATER

Spatiotemporally-Specific Patterns of Dopamine Release Shape Action Selection

Chair: Daniel Covey
Presenters: Christopher Howard, Nick Hollon, Anne Collins, Daniel Covey

Brain dopamine (DA) function controls goal-directed action and its dysfunction is implicated in numerous neuropsychiatric and neurodegenerative disorders. But how region- and temporally-specific patterns of DA release in the striatum differentially shape action selection remains poorly understood. Our panel will discuss cellular and circuit-level mechanisms that control goal-directed actions by modulating DA release dynamics across the striatum. Chris Howard and Nick Hollon will first discuss findings on the role of nigrostriatal DA signaling in instrumental behavior. Chris Howard will present recent work investigating how neurochemically distinct subregions of the dorsal striatum (DS) known as patches (or striosomes) influence striatal DA release and habit formation through inhibitory projections onto midbrain DA cell bodies. Nick will then show that self-initiated goal-directed action also suppresses DA release in the DS according to the action-outcome contingency, even when the outcome of this action is direct stimulation of midbrain DA cell bodies. Their work provides fundamental insight into how nigrostriatal DA pathways guide movement and behavioral sequences.
Annie Collins and Dan Covey will then present recent work showing that distinct neuromodulatory networks differentially influence DA release in the nucleus accumbens (NAc) to shape reward seeking. Annie will discuss how cholinergic interneurons function as a suppressatory gate on reward seeking by locally inhibiting terminal DA release in the NAc. Dan will then close the session by showing that NAc DA release differentially signals past and future reward cost during motivated reward seeking and chronic pharmacological enhancement of endocannabinoid (eCB) signaling stably facilities DA function and motivation.

PANEL • THURSDAY • 7:30 A.M. - 9:30 A.M. • CANYON

Advances in Cell-Type Specific Detection and Manipulation of Neurotransmitters

Chair: David Root

Presenters: Jason Dong, Jonathan Marvin, Dillon McGovern, Michael Tadross

Calcium imaging and channelrhodopsin-assisted electrophysiological methods have greatly advanced understanding of the neuronal activity patterns of genetically-defined neurons during motivated behavior. However, the cell-type specific neurochemical mechanisms that underlie neuronal activity patterns during motivated behavior are unclear. Recently, several neurotransmitter-specific sensors have been engineered with cell-type specific precision. In addition, the recently-engineered DART technology allows for cell-type specific pharmacological manipulation. This panel will present the latest neurotechnology to detect and manipulate specific neurotransmitters as well as present new research on their use during motivated behaviors. Jason Dong, a graduate student in Dr. Lin Tian' s lab will describe the engineering and use of serotonin sensors during motivated behavior and to enable real-time pharmacology for psychedelic discovery. Dr. Jonathan Marvin, Senior Scientist at Janelia Farms, will discuss the protein engineering and development of sensors for glutamate, GABA, ATP, and acetylcholine. Dillon McGovern, graduate student in the Root lab, will present his research recording glutamate and GABA binding on ventral tegmental area glutamate neurons that identifies novel neurochemical mechanisms underlying how these specific neurons signal reward, aversion, and learned predictors of these outcomes. Finally, Dr. Michael Tadross will discuss the engineering and use of DART in multiple cell-type specific populations to regulate behavior under motivated and pathological conditions. Together, this session will demonstrate the utility of a fast-growing toolbox of sensors for chemical transmission that is well poised to permit direct functional analysis of how the spatiotemporal coding of chemical input signaling mediates the plasticity and function of brain circuits.

PANEL • THURSDAY • 7:30 A.M. - 9:30 A.M. • CHEYENNE

Neuronal Ensembles and Engrams in Appetitive and Aversive Behaviors

Chair: Bruce Hope

Presenters: Denise Cai, Leslie Whitaker, Melissa Malvaez, Rajtarun Madangopal

Learned associations between cues and outcomes guide both appetitive and aversive behaviors. Learning induces highly specific long-lasting changes (engrams) in sparsely distributed patterns of neurons (neuronal ensembles) that encode highly specific learned associations. Identifying the specific neural

elements that mediate the formation and maintenance of these engrams and ensembles will allow us to understand and perhaps ameliorate learning-related disorders such as substance use disorders and PTSD. Bruce Hope will introduce a panel describing recent work using the latest chemogenetic and optogenetic methods to manipulate ensembles, and calcium imaging and electrophysiological methods to identify and characterize functional alterations within neuronal ensembles that encode appetitive and aversive learned associations. Denise Cai will discuss how enhancing the valence of a memory leads to increased retrospective linking through overlapping neuronal ensembles shared by two memories that link a predictive cue with the outcome. Leslie Whitaker will present her results showing electrophysiological and molecular alterations that comprise the engram in PFC neuronal ensembles that encode drug-based associative learning. Melissa Malvaez will present data demonstrating the doubly dissociable function of lateral and medial orbitofrontal cortex projections to the basolateral amygdala (BLA) in reward value encoding and retrieval, respectively, as well as the BLA output neurons responsible for using this information to guide adaptive reward pursuit decisions. Rajtarun Madangopal will present ongoing work aimed at longitudinal monitoring of neural populations in vivo in rats during unrestrained operant behaviors. He will also discuss new approaches to permanently label these populations in an activity-dependent manner using CaMPARI for ex vivo analysis of cellular and molecular alterations.

PANEL • THURSDAY • 7:30 A.M. - 9:30 A.M. • DUNRAVEN/OBSIDIAN

Après Concussion: Addiction-Related Sequelae of Traumatic Brain Injury

Chair: Christopher Olsen
Presenters: Alana Conti, Christopher Olsen, Zachary Weil, David Pennington

Traumatic brain injury (TBI) and substance abuse are highly comorbid diseases. This panel will explore behavioral and mechanistic interactions between traumatic brain injury (TBI) and substance abuse in rodents and humans. Alana Conti (Wayne State University School of Medicine and the John D. Dingell VA Medical Center) will describe the influence of experimental traumatic brain injury combined with opioid exposure (as a model of post-injury pain relief) on oxidative stress and inflammatory outcomes, as they relate to behavioral responding in pain and drug preference assessments. Chris Olsen (Medical College of Wisconsin) will present data demonstrating elevated oxycodone seeking in rats exposed to mild TBI, and neuroimaging correlates of combined injury and opioid exposure. Zachary Weil (West Virginia University School of Medicine) will present data on the neuroinflammatory and neuroendocrine links between early TBI and alcohol-related behaviors later in life. David Pennington (University of California San Francisco and San

Francisco Veterans Affairs Health Care System) will present data on cognitive remediation (Approach Bias Modification) and N-acetylcysteine treatment for improving cognitive function in veterans with comorbid alcohol use disorder and traumatic brain injury.

PANEL • THURSDAY • 7:30 A.M. - 9:30 A.M. • GALLATIN

Opioid Modulation of Striatal Circuitry Drives Diverse Behavioral Adaptions

Chair: William Birdsong

Presenters: Sweta Adhikary, Tracy Fetterly, Aya Matsui, Nicolas Massaly

In this panel we will investigate mechanisms of opioid modulation of inputs to and outputs from the dorsal striatum and nucleus accumbens. In particular this panel of young investigators will discuss how the opioid system can interact with other neuromodulatory systems to affect behavior in the context of food and alcohol consumption and inflammatory pain. First, Sweta Adhikary (Oregon Health & Science University) will discuss how mu opioid receptor activation regulates the release of adenosine at striatal glutamate synapses and how chronic opioid treatment alters striatal micro-circuitry by modulating adenosine's inhibitory tone at both opioid sensitive and insensitive synapses. Tracy Fetterly (University of Michigan) will be discussing the mechanistic actions of insulin on excitatory transmission in the nucleus accumbens (NAc). More specifically, how insulin receptor activation results in decreased presynaptic glutamate release in the NAc via an opioid-receptor mediated mechanism. Furthermore, effects of obesity on the actions of insulin in the NAc will be investigated. Aya Matsui (National Institute on Alcohol Abuse and Alcoholism) will present work investigating the role of opioid receptors in modulating inhibitory transmission from the NAc to the ventral pallidum and how endogenous opioids act in this circuit to regulate alcohol intake. Finally, Nicolas Massaly (Washington University, St. Louis) will discuss how inflammatory pain recruits the dynorphin-kappa opioid system in the nucleus accumbens to dampen animal's motivation for sucrose reward and increase aversive behavior, a hallmark for negative affective states.

Altogether this panel will bring new insights and discuss how the striatal opioid systems, in healthy and pain conditions, regulate food and alcohol intake.

PANEL • THURSDAY • 7:30 A.M. - 9:30 A.M. • GIBBON

A Role for Glia in Neuropsychiatric Disorders

Chair: Michelle Olsen

Presenters: Michelle Olsen, Harry Pantazopoulos, Mikhail Pletnikov, Robert McCullumsmith

Central nervous system glia are key players in healthy central nervous system functioning. A sufficient body of literature now implicates dysfunction of these cells in major depressive disorder, chronic stress, major depression and neurodevelopmental/neuropsychiatric disorders. The current panel proposal focuses on astrocyte and oligodendrocyte dysfunction in neurodevelopmental and neuropsychiatric illness across pre-clinical animal and iPSC model systems as well as human postmortem studies models.

Dr. Olsen will discuss altered astrocyte function in the neurodevelopmental/neuropsychiatric disorder Rett syndrome. Her studies indicate that MeCP2, the transcriptional regulator disrupted in Rett has unique astrocyte molecular targets, including the astrocytic protein Kir4.1. Kir4.1 is a glial specific K+ channel which mediates extracellular K+ homeostasis, a critical protein for regulating extracellular K+ dynamics following neural activity.

Dr. Pantazopoulos will discuss evidence from postmortem human studies, pointing to a role for astrocytes and oligodendrocyte precursors in the pathophysiology of major psychoses. Her studies show that interactions between glial cells, neurons and extracellular matrix are disrupted in schizophrenia and bipolar disorders, potentially impacting synaptic functions.

Dr. Pletnikov will present his recent studies of potential contribution of neuron-astrocyte metabolic coupling to neuronal circuit maturation and cognitive function in a time and brain region-dependent manner. He will discuss data from his lab and others indicating a role for abnormal astrocyte support of neuronal activity could lead to neurobehavioral and cognitive changes consistent with aspects of major psychiatric disorder.

Robert McCullumsmith will discuss the bioenergetic deficits found in iPSC cells derived from postmortem schizophrenic patient brain tissue. His studies demonstrate a central role in disrupted glycolysis in neurodevelopment.

PANEL • THURSDAY • 7:30 A.M. - 9:30 A.M. • LAKE

Schizophrenia: Different Phenotypes/Different Brain Systems

Chair: Matthias Kirschner

Presenters: Neil Cashman, George Foussias, Bratislav Misic, Matthias Kirschner

This symposium is based on the theory that schizophrenia is a progressive early-onset neurodegenerative disease whose expression is shaped by the brain connectome. This model harks back to Kraepelin's conception of Dementia

Praecox: a degenerative disease affecting multiple spheres of cognitive and emotional function. We will review clinical heterogeneity in schizophrenia at from the standpoint of cognitive function, genetics, and brain imaging.
We will introduce the idea of schizophrenia as a neurodegenerative (maybe even a prion) disease! The speakers will provide new information on phenotypic variability in schizophrenia.
Neil Cashman will show that DISC1 co-aggregation with TDP-43 has been found to impair activity-related, dendritic protein translation in frontotemporal dementia (FTD), and may contribute to psychotic features of this neurodegenerative disorder (Endo et al, Biol Psych 2018). The DISC1 interactome includes proteins relevant to neurodegeneration that misfold and propagate in a prion-like fashion. It is possible that DISC1 misfolding, aggregation, and co-aggregation could participate in neurodegeneration as well as schizophrenia.
George Foussias (Behavioural phenotypes of motivation deficits in schizophrenia) will address the motivational deficits. His innovative approach has uncovered distinct phenotypes of reward-based and intrinsic motivation deficits in schizophrenia.
Bratislav Misic (Spatial patterning of tissue volume loss in schizophrenia reflects brain network architecture) will review concepts of network neuroscience, and show that patterns of brain atrophy in large cohorts of schizophrenia patients are consistent with a propagating process. He will show that specific brain networks are vulnerable to the disease.
Matthias Kirschner (Clinical-anatomical phenotypes of schizophrenia) will show that multivariate methods can extract pehenotypic patterns from combined clinical and imaging datasets.

PANEL • THURSDAY • 7:30 A.M. - 9:30 A.M. • LAMAR

A Yardsale of Migraine and Headache Animal Models: New Models and New Developments in Established Ones

Chair: Serapio Baca
Presenters: Amynah Pradhan, Guido Faas, Maggie Waung, Michael Morgan

Migraine and headache are complex neurological disorders that involve a dizzying number of brain and vascular networks. Despite recent advancements, there is presently no cure for migraine and many people with migraine and headache fail to find relief from any current medications. Nonetheless, improvements in understanding migraine and headache pathophysiology have arisen from the use of a number of different animal models that capture a subset of the defining features of the disorder. Or, they have arisen from animal models generated from the known genetic contributions to the disorder. This panel will highlight new developments in established models while also featuring recent research in an invertebrate system. Serapio Baca will provide a brief

overview of the systems and their utility in migraine and headache research. Amynah Pradhan will discuss her timely work on the overlapping mechanisms between opioid-induced hyperalgesia and chronic migraine. Guido Faas will discuss recent technological innovations for the long-term monitoring of cortical spreading depression (CSD) and blood flow in mice. Maggie Waung will discuss her recent work demonstrating that silencing peri-aqueductal grey (PAG) neurons that project to the ventral tegmental area (VTA) relieves headache pain. Last, Michael Morgan will provide molecular and cellular insights on the cholinergic and GABAergic consequences in c. elegans that come from a gain of function mutation found in humans in familial hemiplegic migraine type 1 (FHM1). Collectively these panelists employ a number of behavioral, electrophysiological, optogenetic, and molecular assays in different models to try to understand processes that are relevant to the understanding and treatment of migraine and headache.

Thursday Afternoon Panel Sessions

PANEL • THURSDAY • 4:30 P.M. - 6:30 P.M. • AMPHITHEATER

Big Sky High: Mechanisms of Endocannabinoid System Control of Brain Function and Nociception

Chair: Carl Lupica
Presenters: Carl Lupica, Zsolt Lenkei, Aron Lichtman, Daniel Morgan

Scientific knowledge of the roles for the endogenous cannabinoid (eCB) system in regulating multiple physiological and behavioral processes is expanding at a rapid pace. However, many questions remain as to the mechanisms through which eCBs regulate the physiological and behavioral processes. The answers to these questions are important because they will help determine the therapeutic utility of manipulating the endocannabinoid system in the treatment of neurodegenerative diseases and psychiatric disorders. In this panel we present studies designed to answer both fundamental questions regarding the mechanisms in which the eCB system regulates brain function, as well as how manipulating this system can impact nociceptive behavior associated with cancer treatment. Our first speaker, Carl Lupica (NIDA-IRP), will present data addressing the long-standing problem of how eCBs are released to alter synaptic function in the CNS. He will provide evidence to show that eCBs are found in non-synaptic extracellular vesicles (EVs), and that disruption of the release of EVs can alter effects of ECBs at central synapses. Zsolt Lenkei (INSERM) will discuss the use of ultrafast functional ultrasound (fUS) imaging to localize with high resolution changes in regional brain connectivity caused by cannabinoid receptor activation. Aron Lichtman (Virginia Commonwealth U.) will discuss research examining the use of inhibitors of enzymes of eCB synthesis to ameliorate nociceptive behavior in a mouse model of chemotherapy-induced

peripheral neuropathy. Finally, Daniel Morgan (Penn State U.) will talk about sex differences in responding to cannabinoid agonists in acute and chronic pain associated with cancer treatment.

PANEL • THURSDAY • 4:30 P.M. - 6:30 P.M. • CANYON

Kappa Opioid Receptors: The Multi-Headed Gatekeepers of the Nucleus Accumbens and Motivation

Chair: Jessica Barson

Presenters: Jessica Barson, Anushree Karkhanis, Hugo Tejeda, Elena Chartoff

The kappa opioid receptor (KOR) and its cognate ligand, dynorphin, have canonically been understood to produce negative affective states, via actions in the limbic system. In the nucleus accumbens, KORs are believed to induce these states, in part, by suppressing dopamine release. This panel will describe new research demonstrating that the relationship between accumbal KORs and negative affect is far more multifaceted than originally believed. Jessica Barson will present evidence that behavioral effects of KOR activation in the accumbens shell depend on its rostro-caudal location. She will describe how injection of a KOR agonist leads to opposite effects on anxiety-like behavior and also ethanol drinking when made in the rostral vs. caudal shell. Anushree Karkhanis will show that KOR control of dopamine release in the nucleus accumbens is regionally distinct along the rostro-caudal axis following stress and ethanol exposure. She will discuss how these anatomically-dependent effects of KORs could mediate the effects of dynorphin on affective states and motivation. Hugo Tejeda will describe how stress promotes negative affect via mechanisms that enhance accumbens D1 medium spiny neuron activity, thus promoting dynorphin release and subsequently activating KORs. He will discuss how stress-induced dynorphin/KOR signaling may limit nucleus accumbens cell assemblies that control reward-seeking behavior and adaptive responses to cope with or avoid threats. Elena Chartoff will describe how KOR activation has been shown in males to suppress accumbal dopamine release and trigger depressive- and anxiety-like behavior. She will present evidence in females that shows these effects of KOR activation are blunted compared to males, indicating sex differences in the neural circuits necessary for negative affective states. These presentations will highlight the diverse influences that determine the neurochemical and behavioral outcomes of KOR activation in the nucleus accumbens.

DNA Structure and Function – at the Nexus Between Environmental and Genetic Risk for Neuropsychiatric Disorders

Chair: Amelia Gallitano

Presenters: Amelia Gallitano, Cathy Barr, Madabhushi Ram, Robert McCullumsmith

Recent genome-wide association studies (GWAS) have identified hundreds of genomic loci associated with risk for neuropsychiatric disorders. Yet, the molecular alterations in these regions that increase psychiatric illness risk, and the genes affected by these variations, remain unknown. Moreover, genetics determine only 50 – 70% of psychiatric illnesses susceptibility, implicating environment in the remainder. Thus, the next major challenges in psychiatry are to determine how variations affect the function of genes in these regions, and how environment impacts the genome to alter these processes. The panel will address these questions through four approaches. Dr. Gallitano (University of Arizona) will report novel genes activated in an environmentally responsive biological pathway influencing memory, behavior, and synaptic plasticity. This pathway includes numerous genes that map to the Psychiatric Genomics Consortium (PGC) GWAS loci for schizophrenia and depression. Dr. Barr (University of Toronto) will report on work aimed to identify the impact of genetic variants on neural cell function by CRISPR/Cas9 genome editing experiments that alters genomic regulatory regions associated with schizophrenia, major depressive disorder, and neurodevelopmental disorders. Dr. Madabhushi (University of Texas Southwestern Medical Center) will present work detailing how transcriptional programs that underlie the development of adaptive behaviors, including long-lasting memories, are regulated through the formation and repair of DNA breaks at specific genomic loci, and their implications for neurological disorders. Dr. McCullumsmith (University of Toledo) will report on an environmental model of loss, employing RNAseq, shotgun proteomics, and kinomics approaches to identify the molecular changes that occur in the brain in response to loss following transition from an enriched, to a deprived, environment. The panel will conclude with discussion and questions.

Sex Differences in Neurodevelopmental Abnormalities Arising From Early Life Insults

Chairs: Debra Bangasser, Jared Young
Presenters: Lauren Ellman, Jared Young, Jennifer Honeycutt, Debra Bangasser

The search for novel treatments for psychiatric disorders is hampered due in-part to an incomplete understanding of neural abnormalities of patients. Increasing evidence points toward neurodevelopmental processes being affected that underlie the altered neurobiology observed in adults. Early life insults, such as stress and immune disruptions, drive changes in brain development that increase odds-risk for a psychiatric diagnosis. Importantly, such insults affect males and females differently, likely contributing to sex differences in psychiatric illnesses. This panel will present data from humans and animal models revealing sex differences in neurodevelopmental abnormalities that arise from early life insults. Dr. Ellman will present longitudinal research revealing that exposure to maternal inflammation during gestation elevates depression scores in adolescent offspring in a sex-specific manner. Dr. Young will present research on how altering photoperiod lengths on mice dams, an early-life gestational stressor, results in adult offspring with sex-specific alterations in psychiatric-relevant behaviors, including stress hormones, neuroinflammation, and depressive-like behaviors. Data will be presented on mice with genetic abnormalities that display an altered response to this early-life stressor. Dr. Honeycutt will detail how maternal separation in rats leads to earlier maturation of basolateral amygdala afferents into the prefrontal cortex; a finding seen in both sexes, but that occurs earlier in females. Resting state functional connectivity measures further show lasting alterations in corticolimbic connectivity in females, who appear uniquely impacted by caregiver deprivation. Finally, Dr. Bangasser will detail how exposure of rat pups to a limited resource environment can actually result in sex-specific stress inoculation: promoting resilience of adult males to impulsivity and drug self-administration, while inducing sex differences in neuroepigenetic processes.

Identifying Neurobiological Substrates of Functional Decline to Help Develop Brain-Interventional Approaches in Normal and Pathological Aging

Chair: Natalie Ebner

Presenters: Mara Mather, Nathan Spreng, Jennifer Bizon, Natalie Ebner

Aging is associated with functional decline, with deficits exacerbated in pathological aging. Neuroimaging allows identification of neurobiological substrates of this age- and pathology-related decline and provides brain-interventional opportunities for functional enhancement. Panel experts will present advances from animal and human aging research, integrating innovative neuroimaging, biomarker, and neurophysiological methodologies. Dr. Mather will show that while 'hot spots' of high excitation are maintained in aging, the locus coeruleus is less effective at amplifying frontoparietal attention network activity, reducing older adults' ability to hone-in on what really matters under arousal. She will present results that locus coeruleus volume predicts conversion to Alzheimer's disease. Dr. Spreng will present work integrating cerebrospinal fluid biomarkers, multi-modal neuroimaging, and genomic data to triangulate cell-type specific degeneration of human cholinergic basal forebrain neurons, involved in memory formation, in vivo at stages of Alzheimer's disease preceding cognitive impairment. Dr. Bizon will show that vagus nerve stimulation (VNS) enhances attentional set shifting in aged rodents. She will present data that VNS can restore excitatory/inhibitory dysregulation in aging and will discuss pharmacological and optogenetic methods to determine the role of noradrenergic or cholinergic modulation in VNS-mediated cognitive enhancement. Dr. Ebner will present neurofeedback training data using innovative real-time functional magnetic resonance imaging suggesting that both healthy older adults and Parkinson's disease patients can obtain volitional control over brain activity. She will discuss behavioral benefits on selective attention associated with neurofeedback success. The panel will conclude with a brief discussion integrating the findings in the context of current frontiers and translational impact in research on healthy aging and aging-related disease.

PANEL • THURSDAY • 4:30 P.M. - 6:30 P.M. • GIBBON

Novel Models for Studying Stress Influence on Alcohol or Substance Use Disorder

Chair: Jayme McReynolds

Presenters: Jayme McReynolds, Jessica Loweth, Daniel Manvich, Jeffrey Tasker

Addiction involves interactions among several factors, including stress, that promote drug and alcohol use. However, the involvement of stress in addiction is complex and still poorly understood. This is due in part to the lack of newer behavioral models to examine the various roles for stress in different aspects of addiction. Considering NIDA's request for information on animal models of drug addiction, this panel will highlight novel behavioral models being used to study the influence of stress on drug and alcohol use and seeking. Jayme McReynolds (Marquette University) will discuss how repeated daily stress at the time of drug use can induce an escalation of cocaine intake and increase susceptibility for reinstatement and highlight the involvement of endocannabinoids in these effects. Jessica Loweth (Rowan University School of Osteopathic Medicine) will present data on the effects of chronic stress exposure during early withdrawal on cue-induced cocaine seeking behavior in adult male and female rats, including the influence of the estrous cycle. The effects of cocaine and chronic stress exposure on glutamatergic signaling pathways in the nucleus accumbens and basolateral amygdala will also be discussed. Dan Manvich (Rowan University School of Osteopathic Medicine) will present data using a unique model of psychosocial stress-induced cocaine seeking in rats, where the magnitude of drug-seeking behavior is positively correlated with an active, rather than passive, stress-coping phenotype. Preliminary findings from brain activation mapping studies during psychosocial stress-induced cocaine seeking will also be presented. Jeff Tasker (Tulane University) will present data using a model of escalation of alcohol consumption following predator odor traumatic stress, where traumatic stress suppresses the acute inhibitory synaptic response to alcohol mediated by parvalbumin interneuron inputs to principal neurons of the basolateral nucleus of the amygdala.

PANEL • THURSDAY • 4:30 P.M. - 6:30 P.M. • LAKE

Dynamic Neural Encoding of Real-Time Behavioral State Changes in Response to Fear- and Aversion-Inciting Stimuli

Chair: Lindsay Halladay
Presenters: Jose Rodriguez-Romaguera, Lindsay Halladay, Jonathan Fadok, Robert Rozeske

Appropriate defensive response selection to ensure survival involves a coordinated effort from neural regions associated with both innate and learned fear responding. This panel focuses on dynamic neural encoding of real-time behavioral changes in response to potentially aversive outcomes. Speaker presentations reflect the progression of an organism initially responding to aversive stimuli, then forming an association between stimulus and aversive outcome, selecting an appropriate defensive response, and finally, rapidly discriminating aversive vs safe contexts. Jose Rodriguez-Romaguera (UNC Chapel Hill) used single-cell calcium imaging in freely-moving animals to identify a subpopulation of neurons in the bed nucleus of the stria terminalis (BNST) that modulates rapid changes in physiological arousal during exposure to arousal-inducing stimuli and anxiogenic environments. Lindsay Halladay (Santa Clara University) recorded single units in BNST during cued fear learning and characterized two discrete populations of neurons there: phasic units exhibit robust firing rate changes only during initial cued fear learning and predict subsequent freezing expression, while ramping units exhibit gradual firing rate changes that correlate with fear expression during learning. Jonathan Fadok (Tulane University) examined discrete suites of defense responses elicited by threat imminence. He used cell type-specific perturbations, neuronal recordings, and neuroanatomical tracing to characterize global brain networks mediating the selection and intensity of defensive responses. Finally, Rob Rozeske (McGill University) combined in vivo calcium imaging with a fear conditioning task that permits rapid context 'teleportation'. His results indicate that hippocampal region CA1 contains subpopulations of cells that are activated during transitions into a safe or dangerous context. Together these findings highlight the complex and diverse neural mechanisms underlying the drive to survive.

Regulation of Excitability: From Channels to Diseases

Chairs: Terunaga Nakagawa, Kasper Hansen
Presenters: Kasper Hansen, John Gray, Tija Jacob, Terunaga Nakagawa

Dysregulation of synaptic transmission is implicated in disease etiologies of many neurological and psychiatric disorders. To develop therapeutic agents that mitigate the aberrant regulation in disease states, it is critical to reveal signaling mechanisms of postsynaptic neurotransmitter receptors. With recent advances in proteomics and structural elucidation of the members of NMDA, AMPA, and GABA-A receptors, investigations into their functional modulation are undertaken at an unprecedented precision. In this panel we will focus our discussion on novel signaling pathways and mechanisms that can control excitability via these channels. We will start with introducing new mechanisms on NMDA receptor functional regulation. Dr. Hansen will discuss pharmacological regulation of synaptic transmission in distinct neuronal populations by subtype-specific NMDA receptor glycine site agonists. Dr. Gray will present implications on synaptic physiology mediated by regulation of the NMDA receptor co-agonist D-serine, and discuss its relation to psychiatric disorders. Dysfunction of excitatory synapses occurs in benzodiazepine treatment, but the molecular bases remain elusive. Dr. Jacob will discuss molecular pathways that control synaptic adaptation induced by benzodiazepine tolerance through the action of GABA-A receptors. In AMPA receptors, gating and trafficking is controlled extensively by its auxiliary subunits. Dr. Nakagawa will discuss mechanistic insights on AMPA receptor regulation by auxiliary subunits obtained by cryo-EM and implications on synaptic transmission. This panel will provide a comprehensive discussion on novel aspects of synaptic signaling, thereby providing up-to-date and new perspectives on neurotransmitter receptor from structure-function to physiology.

Poster Abstracts

SUNDAY, JANUARY 26, 2020 • 3:30 P.M. - 4:30 P.M. • JEFFERSON/MADISON

S1. Hypothalamic POMC-Expressing Neurons are Activated by Low-Dose Ethanol

Lauren Hood, Erin Nagy, M. Foster Olive*

Hypothalamic neurons that express proopiomelanocortin (POMC) are important for regulating metabolism and experiencing satiety. The POMC peptide is also a precursor for endogenous opioids such as beta-endorphin, which are implicated in driving addiction and alcoholism. Increased endorphin levels are found in the nucleus accumbens, amygdala, and hypothalamus of rodents after both acute and chronic ethanol exposure. However, it remains unclear how ethanol acts on various endogenous opioid-containing circuits in the brain. The current study investigated the effects of voluntary ethanol intake on POMC neuron activity in the arcuate nucleus of the hypothalamus. Male and female transgenic mice expressing enhanced GFP (eGFP) under the POMC promoter were given free access to 20% ethanol for two hours during the dark phase of their light cycle in a paradigm titled drinking-in-the-dark (DID). After 3 consecutive days of habituation to this procedure, mice were given short access (20 min) to either 20% ethanol, 0.25% saccharin, or water. One hour after the 20-min access period, mice underwent transcardial perfusion, blood sampling for assessment of blood alcohol levels, and brain extraction for immunohistochemical analysis of c-fos expression. Ethanol intake and blood ethanol levels in males were 0.6±0.2 g/kg and 10±5 mM, respectively, and in females were 0.6±0.1 g/kg and 7±3 mM, respectively. The percentages of c-fos expressing POMC neurons were 19.2±2.5% in ethanol-consuming males and 17.3±4.3% in ethanol consuming females, which were significantly greater than those observed in saccharin or water consuming mice. These data suggest a subset of POMC-expressing neurons in the arcuate nucleus are a target of low-dose ethanol when voluntarily consumed.

S2. An Electrochemical Aptamer-Based (E-AB) Biosensor Platform for Real-Time, High Precision Pharmacokinetic and Pharmacodynamic Measurements Within the Brain

Julian Gerson, Philippe Ducharme, Kyle Ploense, Netz Arroyo, Kevin Plaxco, Tod Kippin*

The brain is an incredibly complex signaling organ, simultaneously coordinating the release and detection of multiple chemicals that can exert their impact as rapidly as on the order of tens of milliseconds. As neuroscientists, our ability to understand how the brain works is inherently linked to our ability to detect and manipulate these signals in order to understand their endogenous effects. As such, we are only as strong as the tools available to us. Current techniques are challenged to resolve more than a small number of these signaling molecules, or exogenously administered drugs, on physiologically appropriate timescales. In response to this, our group has developed a novel platform, electrochemical aptamer based (E-AB) biosensors, capable of detecting physiologically relevant ranges of exogenously administered pharmacological agents, as well as endogenously present targets of interest. Here we present three novel implementations of this platform. We have developed and implemented an in brain E-AB sensor capable of detecting serotonin (5-HT) with high specificity in awake, ambulatory subjects. 5-HT is an endogenous neurotransmitter that has critical participation in a wide range brain functions, such as arousal, motivation, learning, and equally has been implicated in disorders, such as depression, anxiety, schizophrenia, addiction, and insomnia. In addition, we have developed and implemented another in brain E-AB sensor for the detection of cocaine levels in the brain, an exogenous psychoactive compound known to strongly influence 5-HT signaling in the brain. Together, these sensors could be used to give us further insight into the impact of cocaine on 5-HT circuitry, as well as the role of 5-HT in the development and persistence of psychostimulant addiction. Lastly, we have adapted an E-AB sensor specific for Vancomycin in the circulatory system (previously reported by our group), for in brain detection. Here we present simultaneous measurements of Vancomycin levels in both the circulatory system as well as the brain at high time resolution (11 seconds) in order to explore drug specific blood brain barrier kinetics.

S3. Perineuronal Net Removal Prior to but Not Following Retrieval Attenuates Cue-Induced Reinstatement in Cocaine Self-Administering Rats

Jereme Wingert, John Harkness, Angela Gonzalez, Ryan Todd, Barbara Sorg*

Repeated cocaine exposure can lead to the formation of persistent drug memories that contribute to drug seeking behavior. The medial prefrontal cortex (mPFC) is instrumental in cocaine-induced drug-seeking behavior

and memory. Here we investigated the impact of removal of perineuronal nets (PNNs) with chondroitinase ABC (Ch-ABC) on cocaine-associated memory reconsolidation. First, we showed that Ch-ABC rapidly degraded PNNs in vivo within 1 hour of injection, suggesting that it may be effective at attenuating reinstatement when injected post reactivation. To explore pre- and post-reactivation Ch-ABC treatment on behavior, rats were trained to self-administer cocaine on a fixed ratio 1 (FR1) schedule of reinforcement for 10 days. One cohort received intracranial Ch-ABC 3 days prior to the reactivation session (pre-reactivation) on the last day of training, while the other received Ch-ABC 90 min after reactivation (post-reactivation). Rats were given a 30 min memory reactivation session using either an FR1 or a novel variable ratio 5 (VR5) schedule of reinforcement for pre-reactivation-treated animals and on a VR5 schedule for post-reactivation animals. The next day, lever-pressing behavior was measured for 30 min during extinction and then 30 min during cue-reinstatement conditions. It was hypothesized that Ch-ABC given either pre- or post-reactivation would disrupt reconsolidation and attenuate cue-induced lever pressing. Ch-ABC did not affect extinction rate in any conditions; however, Ch-ABC reduced cue reinstatement in the pre-reactivation Ch-ABC cohort when memory was reactivated by the VR5 (but not the FR1) session, indicating that memory is reconsolidated only when a novel reactivation session is used. Surprisingly, Ch-ABC given post-reactivation increased cue-reinstatement. Our results suggest that PNNs in the mPFC may be a target for novel therapies in cocaine addiction, but further exploration of the time-dependent differences in outcome is necessary.

S4. Cocaine-Induced Reinstatement Alters Parvalbumin Cells in the Rat Medial Prefrontal Cortex Following Removal of Perineuronal Nets

Angela Gonzalez, Emily Jorgensen, John Harkness, Sue Aicher, Deb Hegarty, Travis Brown, Barb Sorg*

Parvalbumin (PV)-positive cells are GABAergic fast-spiking interneurons that modulate the activity of pyramidal neurons in the medial prefrontal cortex (mPFC) and their output to brain areas associated with learning and memory. The majority of PV cells are surrounded by a specialized extracellular matrix structure called the perineuronal net (PNN). We have recently shown that cocaine exposure and cocaine-associated memories can alter the staining intensity of PNNs and PV intensity in the mPFC. Moreover, we have shown that removal of PNNs with the enzyme chondroitinase ABC (Ch-ABC) in the mPFC prevents the consolidation and reconsolidation of cocaine-associated memories. Here we examined the time course of changes in PV intensity following cocaine-induced reinstatement after removal of PNNs. Rats were trained for cocaine-induced conditioned place preference (CPP) for 6 days.

Rats then underwent extinction training for 8-12 days. After the last extinction training, rats were microinjected with Ch-ABC in the prelimbic (PL) mPFC. Re-exposure to the CPP context occurred 72 hours after the microinjection of the enzyme with a cocaine priming injection (10 mg/kg ip). Rats were sacrificed either 2 hr, 6 hr, or 48 hr following reinstatement. A separate cohort of rats was sacrificed prior to any cocaine re-exposure as a baseline control (t = 0 hr). Brain slices were stained and quantified for PV and PNNs. We are currently measuring the intensity of PV and PNNs and excitatory and inhibitory puncta apposing PV cells surrounded by PNNs. Our preliminary data suggest that PV intensity increases at 2 and 6 hr that normalizes by 48 hr. Our data also indicate that there are changes in the intrinsic firing properties of PV cells 2 hr after cocaine priming. These findings suggest that there are rapid changes in PV content, which may in turn regulate output of the mPFC and reinstatement behavior.

S5. Contributions of Prelimbic-Striatal Circuits to Sex-Based Differences in Risk-Based Choice

Maria Jose Navarro, Michael Saddoris*

Brain regions involved in reward seeking and motivation, such as dorsomedial striatum (DMS) and nucleus accumbens (NAc), are particularly vulnerable to chronic effects of drugs of abuse. Regular use of psychostimulants like cocaine cause striking differences in neural signaling in these regions, such as poor encoding of reward-predictive cues by NAc neurons, and abnormal phasic release patterns of dopamine to similar associative cues. These basic encoding properties in Pavlovian conditioning are thought to contribute to more complex deficits in neuroeconomic choice, such as impulsivity, inflexible cognition and abnormal risk-taking behaviors. However, risk-based choice involves a number of competing processes such as the evaluation of the anticipated reward, the probability and severity of the risk, cost-benefit tradeoff assessments, and updating strategies in the face of payoffs/loss. Little is known which of these discrete processes are impacted by repeated cocaine self-administration in decision-making circuits, or indeed whether these impacts vary between sex. Here, we used the Balloon Analogue Risk Task (BART), a paradigms originally created for human studies, to evaluate these discrete elements of risk-taking behavior impacted by drug experience. BART task provides a distinct model to assess different steps of the decision-making process, as animals must balance a desire to press to earn for more rewards versus escalating risk that the trial will "bust" and erase earned potential rewards. In this task, we recorded simultaneously in prelimbic (PL) cortex and its known striatal targets, NAc and DMS during this task in both male and female cocaine-experienced subjects and drug-naïve controls. Surprisingly, we found significantly greater effects of

sex than drug on this approach, males displaying more risk-taking behavior than females. Subsequent neural analyses will be assessed to understand the individual differences contributing to these behavioral profiles.

S6. KCNQ3 Overexpression Differentially Modulates Cue-Induced Reinstatement of Heroin-Seeking in High- Versus Low-Risk Rats

Britahny Baskin, Kes Luchini, Susan Ferguson*

Opioid addiction is a chronic, relapsing disorder, characterized by bouts of compulsive drug intake, protracted withdrawal states, and a high vulnerability to relapse. Opioid addiction in the United States is a national public health emergency because it is responsible for the deaths of more than half a million individuals since 2000 and there is a lack of pharmacotherapeutics for long-term treatment. Similar to other addictive behaviors, opioid addiction is believed to arise in part due to aberrations within the mesocorticoaccumbens loop, a network involved in associative learning, decision-making, and motivation. Central to this circuit is neurons in the ventral tegmental area (VTA) which are hyperexcited by drug-associated cues following opioid use. The KCNQ2/3 channels expressed on dopaminergic VTA neurons, fine-tune their activity by decreasing excitability and have been associated with drug-craving following alcohol or nicotine use. Although they may regulate long-term neuroplasticity in VTA dopamine neurons following opioid use, the functional role of KCNQ channels in regulating relapse behaviors is unknown. Here we use a model of heroin self-administration in male Sprague-Dawley rats to probe relapse behaviors following extended drug abstinence. Using behavioral metrics from intermittent access, progressive ratio, and extinction sessions, an addiction severity score was calculated for each rat classifying animals into those with that have low or high levels of addiction-like behaviors (low-risk or high-risk). Animals then went through 30 days of forced-abstinence and a virus overexpressing KCNQ3 (or sham) was infused into the VTA to maximally express on the day of their cue-induced reinstatement session. Overexpression differentially modulated heroin seeking causing low-risk animals to increase heroin-seeking compared to sham low-risk animals, while high-risk animals increased responding relative to their sham controls. Tissue was collected following reinstatement sessions to validate viral placements and KCNQ3 expression. These findings will add to our understanding of how KCNQ channels regulate neurons in the VTA following heroin use, and how they regulate cue-induced heroin-seeking following long periods of drug abstinence.

S7. Open Board

S8. Gut Microbial Compositions Associated With Cocaine Self-Administration in Adult Male Rats

*Gregory Suess, Giordano de Guglielmo, Olivier George, Benoit Chassaing, Kyle Frantz**

Bacterial communities in the gut participate in a gut-brain axis that influences the nervous system. Disruption in microbial composition is associated with neuropsychiatric disorders, including drug abuse. It remains unknown, however, whether gut microbial profiles can predict an addiction phenotype before it emerges, or reflect drug experience after it occurs. This study tested the hypothesis that the gut microbiota can predict and reflect susceptibility to cocaine reinforcement, using behavioral data and biological samples from the Cocaine Biobank. Adult male rats were catheterized and allowed to acquire lever-pressing maintained by iv cocaine infusions in 2-hr daily sessions (10 days), followed by progressive ratio (PR) testing. Rats were transitioned to long-access daily sessions (6-hr each, 14 days), also followed by a PR test and alternating blocks of footshock testing, long-access, and PR. Fecal samples were collected at three time points, prepared for Illumina sequencing of bacterial 16S rRNA genes, and analyzed for diversity (QIIME 1.9.0). As expected, rats varied in levels of cocaine-related behavior, such that a quartile split identified high and low responders on each measure and an overall addiction index. Although beta diversity at baseline did not predict membership in high or low addiction quartiles, the genus Allobaculum was over-represented in high responders, whereas Akkermansia muciniphila was over-represented in low responders. After long-access, bacterial communities did cluster by high vs. low addiction index, and again the genus Allobaculum was over-represented in high responders. Alpha diversity and functional impact of these differences are under investigation and will expand these findings. Identification of specific bacterial groups associated with high vs. low cocaine responsivity highlights new approaches to prediction and treatment of addiction, as pre- and probiotic therapies might promote a healthy gut and reduce addiction.

S9. Synthetic Cathinone Mephedrone Causes Chronic Leakage of the Blood Brain Barrier by Downregulation of Membrane-Bound Claudin-5

Tetyana Buzhdygan, Scott Rawls, Servio Ramirez*

Synthetic cathinones, such as mephedrone, are an emerging class of designer drugs consumed for psychostimulant and hallucinogenic effects. Recently in the US, the use of synthetic cathinones (bath salts) have dramatically increased, especially among adolescent and young adult populations. Spike of

overdose-related fatalities and adverse effects, including severe brain edema and vascular damage, calls for detailed investigation of the effects of cathinones on cerebral microvascular endothelial cells
We investigated the effects of mephedrone, a synthetic cathinone that is most frequently found in the designer drug formulations linked to the most adverse complications, on the expression of tight junction proteins and the integrity of the endothelial cell monolayer.
We showed that exposure of fetal human brain microvascular endothelial cells (fHBMVEC) to mephedrone resulted in the significant loss of membrane-bound, but not cytosolic fraction of the claudin5 protein (-52.5%, at 24hs). Additionally, functional analyses revealed that mephedrone caused dramatic loss of BBB integrity as measured by transendothelial electrical resistance (-50% from untreated, at 24hs). Chronic exposure to the mephedrone caused a 5-fold increase in the permeability for small (3kDa) but not large sized molecular weight tracers (40kDa and 70kDa FITC-dextran), suggesting enhanced paracellular route.
To date, these are the first studies to report that mephedrone causes endothelial damage and BBB leakiness thereby likely affecting the capacity of the BBB to protect the brain from bloodborne solutes and pathogens. Moreover, our data suggest that cathinones may contribute to drug use-associated CNS infections and neuroinflammation.

S10. Pharmacotherapy Prescribing Patterns in Alcohol Use Disorder (AUD) for Patients Enrolled in the Riahealth Treatment Program (RHTP)

John Mendelson, Julien Stainback, Robert Nix, David Deacon*

Background: Despite many safe and effective AUD pharmacotherapies little is known about anti-alcohol prescribing practices. For most diseases, combination pharmacotherapies are superior to monotherapy yet there are few reports on the use of rational drug combinations in AUD. Here we report the rate, duration and clinical outcomes for anti-alcohol drugs prescribed to patients treated for AUD by RiaHealth. Methods: The RHTP is an AUD telehealth treatment program deployed on smartphones. Alcohol use is quantified with 1-2X/day breath alcohol concentrations (BAC) and patients are treated with medications and coaching. Prescription data were obtained through the Ria application and EHR interfaces which tracks all prescribing to Ria patients. Prescribing of Naltrexone (NTX), acamprosate (ACAM), gabapentin (GABA), baclofen (BAC), and topiramate (TOP) were assessed. Results: From 1/2017-9/2019 816 Ria patients were prescribed anti-AUD meds. At treatment initiation NTX was prescribed to 83.1% followed by GABA (7.6%), NTX-GABA (4.0%), ACAM (2.57%) Baclofen (0.98%) and TOP (0.86%). At 6 months NTX has decreased to 67.61% and NTX-GABA had increased to 12.68%, ACAM

decreased to 2.35%, Baclofen increased to 2.35% and TOP increased to 1.41%. At 6 months, 47% of patients remain in treatment and mean BAC declined from 0.08 to 0.03 g/L (66%). Non-drinking days increased from 1.8 to 3.9 days/week. Conclusions: Medication management in AUD is effective, safe and well tolerated and can be improved with telehealth. In the Ria cohort NTX is the most commonly prescribed monotherapy and NTX-GABA is the most commonly prescribed combination. NTX-GABA combinations appear safe and well tolerated but more research is needed to assess therapeutic switching and synergy. Conflict of Interest: All authors are employees of Ria Health

S11. Decoding Impulsive Decision-Making: Toward Understanding No Friends on Powder Days

*Lucas Dwiel, Aboubacar Cherif, Alan Green, Wilder Doucette**

Impulsive decision-making (IDM) is observed across psychiatric disorders, from ADHD and bipolar to substance use disorders. Variation in IDM can be measured in animals and humans using the delay discounting task (DDT). In patients, high impulsivity relates prospectively to problematic behaviors—gambling, substance use, violence, and suicide—and also predicts non-response to treatment and risk of relapse of the underlying psychiatric disorder. In order to develop personalized treatments that target IDM at a neural systems-level, the known correlation between neural oscillations and DDT performance needs to be more rigorously evaluated. We determined if neural oscillations (local field potentials-LFP) recorded from the cortical-striatal system (known to regulate IDM) could predict innate and stimulation-induced variation in DDT performance. Male and female Sprague-Dawley rats were trained in the DDT, implanted with stimulation and recording electrodes (targeting the infralimbic cortex, orbitofrontal cortex, nucleus accumbens shell and core), and LFPs were recorded in neutral contexts as well as during the DDT (with and without deep brain stimulation). LFP features of power and coherence were used as predictors in machine learning models to classify delay discounting performance (average performance across sessions - trait; session to session performance - state; or trial-to-trial choices). We found that the information about trait and state impulsivity resided mostly in measures of connectivity between brain regions, whereas the information about trial-to-trial decision making was reflected in LFP power. Overall, low frequency (delta and theta) LFP features contained the most information about IDM and stimulation targeted to the infralimbic cortex modulated low frequency LFP features resulting in altered DDT performance. Overall, this data goes beyond correlation to link low frequency features of neural oscillations to impulsive decision-making.

S12. The Immediate Response to Trauma in Adulthood Combined With Early Life Stress Predicts Development of Post-Traumatic Stress Disorder

Felicia Gould, Gabrielle Hodgins, Philip Harvey, Mackenzie Jones, Vasiliki Michopoulos, Barbara Rothbaum, Kerry Ressler, Charles Nemeroff*

Although many reports have documented the relationship between early life stress (ELS) and development of later life psychopathology including Post-Traumatic Stress Disorder (PTSD), few prospective studies of civilians with a history of ELS immediately after trauma exposure have been conducted. Identification of individuals at greatest risk for the development of PTSD likely could lead to early interventions averting its development of PTSD. The present study aimed to determine whether participants with a history of ELS would differ in their vulnerability to PTSD following a Criteria A traumatic event. Further, we aimed to examine the immediate severity of psychological symptoms characteristic of PTSD and determine whether the severity of these reactions predicted development of PTSD. Participants (N=712) were recruited from the Emergency Departments at Jackson Memorial Hospital in Miami and Grady Memorial Hospital in Atlanta immediately following a traumatic experience. Follow-up assessments were conducted at 1-, 3-, and 6- months post-trauma. Early life trauma predicted immediate PTSD-related reactions, which in turn predicted the persistence of PTSD symptoms. PTSD severity at each assessment was the only predictor of PTSD severity at later follow-up. Overall, the current findings suggest that the initial trauma reaction is a strong predictor of PTSD development, which is predicted by early life trauma experience severity.

S13. Behavioral Adaptations in a Relapsing Mouse Model of Colitis

Chelsea Matisz, Aaron Gruber*

Inflammatory bowel disease (IBD) is characterized by relapsing periods of gut inflammation, and is comorbid with depression, anxiety, and cognitive deficits. Animal models of IBD that explore the behavioral consequences almost exclusively use acute models of gut inflammation, which fails to recapitulate the cyclic, chronic nature of IBD. This study sought to identify behavioral differences in digging, memory, and stress-coping strategies in mice exposed to one (acute) or three (chronic) cycles of gut inflammation, using the dextran sodium sulfate (DSS) model of colitis. Similar levels of gut pathology were observed between acute and chronically exposed mice, although mice in the chronic treatment had significantly shorter colons, suggesting more severe disease. Behavioral measures revealed an unexpected pattern in which chronic treatment evoked fewer deficits than acute treatment. Specifically,

acutely-treated mice showed alterations in measures of object burying, object recognition, object location memory, and stress-coping (forced swim task). Chronically-treated animals, however, showed similar alterations in object burying, but not the other measures. These data suggest an adaptive or tolerizing effect of repeated cycles of peripheral gut inflammation on mnemonic function and stress-coping, whereas at least some other behaviors continue to be affected by gut inflammation. We speculate that the normalization of some functions may involve the reversion to the bassline state of the HPA axis and/or microglia, which are both activated by the first exposure to the colitic agent.

S14. Unrestricted Chemogenetic Activation of Norepinephrine Neurons Impairs Attention in the Mouse Continuous Performance Test (rCPT)

Andreas Sørensen, Leonie Posselt, Søren Jørgensen, Ulrik Gether*

The prefrontal cortex (PFC) is known to be an important area regarding impulsivity and attentional control, and believed to be substantially influenced by norepinephrine (NE) and dopamine (DA) levels. The popular inverted U-shaped theory of attention argues that optimal attentional performance depends on balanced levels of NA and DA signaling in the PFC. While previous studies have consistently demonstrated that lack of NA signaling impairs attention, it remains unknown how such cognitive performance is influenced by excessive NE levels. In this study, we took advantage of the excitatory Dq-DREADD, representing a chemogenetic tool that allows powerful control of neurons in vivo, to address how visual attention in the rCPT is influenced during selective activation of NE neurons. To restrict the manipulation towards locus coeruleus (LC)-PFC projecting neurons, we applied a dual viral approach using retrogradely transported CAV2-Cre vector injected into PFC and Cre-dependent AAV vector expressing Dq-DREADD injected into LC. While Dq-DREADD expression was clearly observed in LC in this case, activation of NE neurons did not induce any effects on attentional behavior. On the other hand, if the Dq-DREADD manipulation was directed towards all NE neurons in the LC, attentional performance was severely impaired. This effect was dose-dependent (i.e. CNO) and did not influence any gross motor functions in the rCPT, suggesting that optimal NE signaling is also required elsewhere than PFC for appropriate attentional performance.

S15. Examining the Mechanisms of Spatial Working Memory Encoding and Retrieval in the Prefrontal-Reuniens-Hippocampal Network

John Stout, Amy Griffin*

Spatial working memory (SWM) requires interactions between the medial prefrontal cortex (mPFC) and dorsal hippocampus (dHPC) that are supported in part by connections via the nucleus reuniens (Re). While much work has focused on how the mPFC and dHPC synchronize during SWM tasks, it is unknown how these regions differentially interact with the Re during the encoding and retrieval of spatial memories. To this end, we used multi-site recording techniques while rats performed a T-maze delayed non-match to position (DNMP) task and assessed how mPFC-Re-dHPC interactions differed between the sample ('encoding' dominant) and choice ('retrieval' dominant) phases. We focused our analyses in the epoch surrounding the entrance to T-junction, the location that corresponds to a left/right decision-action, and provide behavioral metrics that solidify the examination of this location. First, we replicate that mPFC-dHPC theta coherence is higher on the choice phase when compared to sample phase (Jones and Wilson, 2005; Sigurdsson et al., 2010; O'Neill et al., 2013) and demonstrate that dHPC-Re fast gamma coherence is comparably higher on the sample phase. Then, we examined how coherence changed between task phase as rats approached and entered the T-junction. Prior to T-entry, we found that the mPFC-dHPC and mPFC-Re groups exhibited higher theta coherence during choice phase with respect to sample phase. For the dHPC-Re group, fast gamma coherence was again found to be comparably higher during the sample phase, while slow gamma coherence was higher during choice phase. Finally, we used granger prediction to show a theta-specific mPFC-to-Re-to-dHPC lead relationship during memory retrieval. Our coherence results provide novel insight into how the mPFC-Re-dHPC network synchronizes to support the encoding and retrieval of spatial memories while our granger findings support the hypothesis that mPFC-Re projections may support the retrieval of SWM (Hallock et al., 2016).

S16. Sleep Disturbances in Mice During Chronic THC Administration and Abstinence

Andrew Kesner, Karina Abrahao, Matthew Pava, David Lovinger*

The diagnosis of cannabis withdrawal is contentious because reliable, objective measures of withdrawal from delta-9-tetrahydrocannabinol (THC), the major psychoactive compound in cannabis, are generally difficult to observe. A known consequence of chronic cannabis use in humans is altered sleep, and sleep disturbances are often cited as a primary withdrawal symptom during cannabis abstinence. Our lab has previously reported a role for endogenous cannabinoid

signaling in sleep stability in mice, and in the current study we aimed to determine if THC withdrawal-induced changes in sleep can be modeled in rodents. Using electrocorticogram and electromyogram recordings from chronically implanted mice combined with our fully automated sleep analysis system to score sleep before, during, and after chronic injection of either THC or vehicle control, we find that polysomnographic measures in mice treated with THC indeed mimic clinical observations of altered sleep architecture in human cannabis users. In particular, measurements obtained over six days following cessation of THC treatment revealed that time spent in NREM sleep was reduced largely because of a decrease in NREM bout duration. Additionally, rapid eye movement (REM) sleep was reduced on the first day of acute THC administration and was enhanced 6 days following treatment. The augmentation in REM during the abstinence phase of the experiment could be due to an increase in the number of REM bouts, and this effect persisted throughout the 6 days of abstinence. None of these changes were observed in controls. Paradoxically, the power of delta oscillations was no different between THC and controls during the first day of abstinence, but THC mice displayed markedly less delta power by the last day of abstinence. This suggests that impairment of processes contributing to slow oscillations in the cortex gradually begins to manifest over recovery from chronic THC exposure. To our knowledge, this is the first murine model of a directly translatable non-precipitated cannabis withdrawal symptom. These data open the door for pre-clinical research efforts to study, and potentially treat, a primary withdrawal symptom of cannabis use disorder.

S17. Mesoscale Collective Action in the Hippocampus: A Thermodynamic Modeling Approach

Alex Sheremet, Yu Qin, Andrew Maurer*

Of the three scales of brain activity (micro-, meso- and macro-scale), mesoscopic activity is the least studied. In the cortex, mesoscopic collective action (MCA) manifests as propagating waves (e.g., Muller et al., 2018). Dismissed often as marginally-significant neuron synchronization, MCA may in fact be the main function of the cortex, as suggested by the non-hierarchical (isotropic and homogeneous) structure of cortical layers, which favors MCA over hierarchical microcircuit activity. This is consistent with the conjecture that physical structures underlying cognition resemble biological systems, with no design and no a priori function (Edelman and Gally, 2001). As such, collective action might play an essential role in the integration of brain activity (e.g., Freeman 2010). Despite a few initial insights (Wilson and Cowan 1973, 1974; and others) a consistent theory for MCA dynamics is still lacking. Because the mesoscale is macroscopic with respect to microscopic processes, the wealth of knowledge accumulated about microscopic physics cannot be directly

extended to mesoscopic processes. We propose that the weak turbulence theory (Zakharov, 1992) could provide the theoretical framework for studying self-sustained MCA dynamics. Turbulence describes the internal energy balance in nonlinear multi-scale systems with a large number of components. Nonlinear interaction between scales results in cross-scale flows of energy and other conserved quantities, known as the "turbulent cascade" (Richardson, 1922; Kolmogorov, 1941). We show that the observed evolution of MCA energy balance (LFP spectra and bispectra) in the hippocampus are consistent with mesoscopic weak turbulence. We derive the governing equations in a general conservation form, that generalize existing models (Wilson-Cowan, 1974, Wright and Liley 1995; and others). We derive dynamical equations for the evolution of the power spectral density, and investigate their averaged (kinetic) behavior. The turbulent model predictions of the theta-gamma phase coupling characteristics are consistent with observations. Turbulence holds the promise to provide a consistent theoretical framework for modeling hippocampal energy processes, including the persistent question about the significance of power law spectra and their slopes.

S18. Effects of a Natural Anti-Inflammatory Agent in a Model of Alzheimer's Disease

Jason Eriksen, Tasha Womack*

Alzheimer's disease (AD) is an incurable neurodegenerative disorder that is the most common cause of dementia in aged populations. A substantial amount of data demonstrates that chronic neuroinflammation can accelerate neurodegenerative pathologies, while epidemiological and experimental evidence suggests that use of anti-inflammatory agents may be neuroprotective. In AD, chronic neuroinflammation results in the upregulation of cyclooxygenase and increased production of prostaglandin H2, a precursor for many vasoactive prostanoids. While is well-established that many prostaglandins can modulate the progression of neurodegenerative disorders, little is known about the role of prostacyclin (PGI2) in the brain. We have conducted studies to assess the effect of elevated prostacyclin biosynthesis in a mouse model of AD. Upregulated prostacyclin expression significantly worsened cognitive abnormalities, accelerated amyloid pathology, and damaged the neurovasculature. PGI2 overexpression selectively increased soluble amyloid-β 42 production, total amyloid accumulation, and burden. PGI2 altered microvessel length and branching, and PGI2 expression in combination with amyloid was more detrimental than amyloid expression alone. In vitro studies demonstrated that increased prostacyclin signaling inhibited microvessel formation and selectively altered gamma secretase subunit expression. Our findings demonstrate that chronic prostacyclin expression plays a novel and unexpected role that hastens the development of the AD phenotype.

S19. Open Board

S20. IRF8 ASOs Modulate Microglia Responses to an Inflammatory Insult

Fredrik Kamme, Christine Hong, Curt Mazur, Holly Kordasiewicz*

Microglia have become of central interest in a range of neurodegenerative, traumatic and affective disorders. A rapidly growing body of literature has demonstrated a range of microglial activation states and functions in both humans and experimental animals.

Antisense oligonucleotides (ASOs) reduce target protein expression by hybridizing to the target RNA and recruiting RNAseH1, resulting in the cleavage and degradation of the target RNA and reduction of expression of the protein. As pharmacological agents, ASOs exhibit high target specificity and an ability to target most RNAs. Together with a rapid development path for ASO therapeutics, ASO technology is a unique platform to explore biology in experimental animals as well as translating new discoveries into human drugs. We have developed ASOs for mouse IRF8 to explore the role of this central transcription factor in microglia responses to injury and disease. IRF8 ASOs were tested in a model of systemic inflammation, triggered by an intraperitoneal LPS administration. After immune challenge, microglia were isolated and analyzed by RNA sequencing. As part of the evaluation, we characterized non-target sequence dependent effects of ASOs on microglia in vivo.

The results show that ASO effects on microglia in vivo are target-sequence specific, demonstrating that ASOs are a suitable platform to modulate microglia in vivo. Knockdown of IRF8 was efficient, long lasting and had significant effects on microglia inflammatory responses to a systemic LPS challenge.

S21. Fox DEN: Novel Data Sharing Platform for Sharing Patient Reported Health Information and Genetic Data From the Largest Parkinson's Cohort Worldwide

Luba Smolensky, Ninad Amondika, Lindsey Riley, Karen Crawford, Scott Neu, Caroline Tanner, Ethan Brown, Monica Korell, Vanessa Arnedo*

Fox Data Exploration Network (DEN): Novel data sharing platform for sharing patient reported health information and genetic data from the largest Parkinson's disease cohort worldwide.

Parkinson's disease (PD), which is the second most common neurodegenerative disease, has a wide range of phenotypes and the rate of progression varies significantly among the affected. Research data from observational studies, particularly those with remote data collection, offer a mechanism to study the heterogeneity and variability in disease.

To this end, patient-reported outcome data and genetic data from Fox Insight (FI), an online study of more than forty thousand people with and without PD, are centralized in the Fox Data Exploration Network (DEN) platform (https://foxinsight-info.michaeljfox.org) and available to researchers. Within the platform, researchers may explore and visualize more than 2,400 self-reported health attributes. In addition, Fox DEN allows researchers to define different sub-cohorts using multiple variables, as well as perform different types of statistical analyses. Researchers are encouraged to use the analysis tool for cohort building and exploratory statistical modeling. Fox DEN also serves as the data download mechanism for researchers who prefer to conduct analyses on the cohort data using external statistical tools.

In more detail, Fox Insight (FI) is an online study which integrates regularly administered validated patient-reported outcomes (PRO) instruments and novel PD-related questionnaires. The surveys follow a regular cadence and pattern dependent on the participant's self-reported diagnosis. Genetic data collection in people with PD (PwP), and one-time surveys focused on specific topics also complement the study.

The Fox Insight cohort consists of 72% PwP with a mean age of 65.8, and mean disease duration of 6.61 years. More than 5450 participants have linked their genetic information through 23andMe.

S22. GABA and Glycine Neurons From the REM Sleep Controlling Ventral Medullary Region Inhibit Hypoglossal Motoneurons: A Mechanism for Obstructive Sleep Apnea

David Mendelowitz, Olga Dergacheva*

Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive sleep related losses of upper airway patency that occur most frequently during rapid eye movement (REM) sleep. Hypoglossal motorneurons (HMNs) play a key role in regulating upper airway muscle tone and patency during sleep. REM sleep active GABA and glycine neurons in the ventral medulla (VM) induce cortical desynchronization and skeletal muscle atonia during REM sleep; however, the role of this brain region in modulating hypoglossal motor activity is unknown. We combined optogenetic and chemogenetic approaches with in-vitro and in-vivo electrophysiology, respectfully, in GAD2-Cre mice of both sexes to tests the hypothesis that VM GABA/glycine neurons control the activity of HMNs and tongue muscles. Here we show there is a pathway originating from GABA/glycine neurons in the VM that monosynaptically inhibits brainstem HMNs innervating both tongue protruder genioglossus (GMNs) and retractor (RMNs) muscles. Optogenetic activation of ChR2-expressing fibers induced a greater postsynaptic inhibition in RMNs than in GMNs. In-vivo chemogenetic activation of VM GABA/glycine neurons produced an inhibitory effect on tongue electromyographic

(EMG) activity, decreasing both the amplitude and duration of inspiratory-related EMG bursts without any change in respiratory rate. These results indicate that activation of GABA/glycine neurons from the REM VM inhibits tongue muscles via a direct pathway to both GMNs and RMNs and this inhibition likely plays an essential role in REM sleep associated upper airway obstructions that occur in patients with OSA.

S23. Histological Evidence for Diffusion Rather Than Convective ("Glymphatic") Bulk Flow of Solutes in the Cerebrospinal Fluid (CSF)

*Miles Herkenham**

Cerebrospinal fluid (CSF) is formed in the choroid plexus and flows through the ventricles, subarachnoid spaces, and interstitial spaces, eventually being cleared into the bloodstream. Solutes in the CSF travel throughout this continuous compartment, which is important for two reasons. First, solute clearance from the brain is important for removal of toxic molecules. Second, neuroactive substances, released at specific sites are also suggested to reach respective distant target cell receptors by diffusion through the extracellular spaces (termed "parasynaptic communication" or "volume transmission").

In 2000, we published a histological demonstration of CSF flow of large-molecular-weight solutes from the ventricles into brain's interstitial spaces (Proescholdt, Neuroscience; 95: 577-92). The tracer [C-14]inulin was delivered via cannulas into the lateral ventricle of rats. Five minutes after infusion, tracer could be seen by autoradiography to rapidly travel throughout the ventricles and subarachnoid spaces, and from these locations, it diffused into the interstitial spaces. By 30 min, tracer had moved into the parenchyma, and by 4 h, the brain was filled with tracer. Perivascular travel was observed, but it was not a major contributor to the distribution.

In 2012, Nedergaard's group published on CSF flow using fluorescent dextran injected into the ventricles and failed to see diffusion but rather saw mainly perivascular flow (Iliff, Sci Transl Med; 4: 147ra111). Based on this and the involvement of aquaporins on astrocyte end feet, they proposed "glymphatic flow" of convective CSF flow.

Since then, there has been controversy over whether CSF flow through the extracellular spaces is convective or diffusive. The pattern of inulin flow clearly supports the diffusive flow interpretation. Apparently inulin, a 5 kDa inert carbohydrate, is a better marker of interstitial transport than large dextrans, which can be pinocytosed during transport.

S24. Late Perampanel Treatment Stops Midazolam-Refractory Seizures in an Experimental Model of Status Epilepticus

*Jerome Niquet, Ireri Franco Estrada, Claude Wasterlain**

Objective: To assess the effectiveness of perampanel, a specific antagonist for AMPA-type glutamate receptors, as a second-line treatment of benzodiazepine-unresponsive Status Epilepticus (SE).
Background: SE responds poorly to benzodiazepines, especially when treatment is delayed. Experimental data show that SE causes an early maladaptive internalization of synaptic GABAA receptors, which may explain benzodiazepine pharmacoresistance, along with a migration of NMDA and AMPA receptors (AMPAR) towards synapses, increasing glutamatergic excitation. Topiramate, an AMPAR antagonist, is often effective in refractory SE, and the stronger AMPAR antagonist perampanel deserves evaluation in the treatment of SE.
Design/Methods: SE was induced in adult male Sprague-Dawley rats by high-dose lithium/pilocarpine, and EEG/video was recorded for 18 hrs. Midazolam (1 mg/kg; ip) was injected 40 min after SE onset. Perampanel (0.5, 1 or 2 mg/kg, ip) or valproate (270 mg/kg) was injected 20 min following midazolam if SE continued.
Results: During the first hour following treatment with perampanel 2 mg/kg (−84 ± 314; $p<0.0001$) or 1 mg/kg (170 ± 410; $p<0.01$), but not valproate 270 mg/kg (453 ± 393, NS), EEG power was decreased compared to midazolam alone (671 ± 208). Perampanel 2 mg/kg (median -514; interquartile range: -1072 to -73; $p<0.001$) or 1 mg/kg (207; -675 to 758; $p<0.05$), but not valproate 270 mg/kg (1027; 396 – 3346, NS), also significantly reduced the EEG power integral over the 6 h posttreatment when compared to midazolam alone (2407; 1557 to 3813). In addition, perampanel 2 mg/kg reduced the time needed for EEG amplitude to decline to twice the pre-seizure baseline (median = 11 min; interquartile range: 6 min – 31 min), compared to midazolam (42 min; 33-77 min; $p < 0.05$), suggesting earlier SE termination.
Conclusions: Perampanel is potent in stopping midazolam-refractory SE even when given 60 min following SE onset in this animal model of severe SE.

S25. Distinct Properties of GABA-A Receptors at Synaptic and Extraysnaptic Sites Shape Circuit Patterns During Seizure Evolution

*David Naylor**

GABA-ARs with gamma2 subunits mediate phasic inhibitory postsynaptic currents (IPSCs) in hippocampal granule cells to brief high concentration transmitter release and rapidly desensitize to low-level tonic or brief

hi-frequency pulsatile GABA exposure. Conversely, extrasynaptic GABA-ARs with delta subunits are non-desensitizing, have greater GABA affinity, and are responsible for tonic inhibitory currents in response to low concentrations of extracellular GABA, but also detect synaptic 'spillover'. With convulsant stimulation and seizure initiation, loss of synaptic inhibition occurs with increases in extracellular GABA (~1uM). Computational models of GABA-ARs optimized to fits of synaptic IPSCs, extrasynaptic tonic currents, and multisynaptic evoked IPSCs simulated GABAergic responses for different circuit conditions. Synaptic receptors desensitize with 90% loss of inhibition at 160 Hz after 100 msec, simulating epileptic 'fast ripples'. Recovery from desensitized states occurs by 10 sec, but superimposed low frequency activity (~0.5 Hz) and/or low level GABA (< 1uM) sustains the loss of synaptic inhibition keeping a significant proportion of postsynaptic GABA-ARs desensitized. Composite models of synaptic and extrasynaptic GABA-ARs show hi-frequency stimulation promotes GABA spillover, and only a few extrasynaptic delta subunit-containing receptors (~ 4 per synapse vs. 36 postsynaptic GABA-ARs) account for 60% of the current of evoked IPSCs, prolonging and broadening the spatial extent of synaptically-released GABA and favoring network slowing. At 3-6 Hz, 10-20 % of synaptic GABA-ARs remain desensitized sustaining inhibitory loss while spillover to extrasynaptic GABA-ARs supports hypersynchronous oscillations. In summary, evidence supports a mechanism of seizure evolution with initiation by fast-rhythmic activity and loss of synaptic inhibition progressing to slowed synchrony, mediated by a dynamic shift of activation from synaptic to extrasynaptic GABA-ARs.

S26. Development of a Novel Locomotor Behavioral Assay to Evaluate the Efficacy of Neurosphere-Mediated Regeneration following CNS Injury

Taylor Schanel, Melanie Rojas Hammani, Scarlyn De Los Santos, Raeden Gray, Elizabeth Batsel, Sean Mondesire, Martin Oudega, Jeffery Plunkett*

Development of suitable locomotor assays to assess functional recovery following central nervous system (CNS) trauma can be an invaluable tool to an investigator. Adult zebrafish (Danio rerio) has proven in recent years to be a model system that can be useful to evaluate not only mutational defects of the CNS but to also study perturbations involving direct injury or trauma. Our laboratory has developed a locomotor assay to study fish locomotor swimming movement in a current of water. Fish naturally swim in currents to maintain physiological levels of oxygen in the blood and our assay exploits this natural tendency. Once a baseline of current swimming was established, we performed a 2mm deep traumatic brain injury (TBI) in the brainstem of an adult fish. Our data show that there is a significant deficit in current swimming through

approximately 7 days at which time recovery towards baseline behavioral swimming levels commences. Next, we challenged the trends of recovery seen in the baseline injury through transplantation of characterized stem neurospheres. We developed the approximately 100 micrometer neurospheres in rotating in vitro aggregate cultures. Once characterized using the neural progenitor marker, neuroD1, specific quantities of aggregates were transplanted into the TBI site. Initial data indicate that transplantation of neurospheres may alter the pathway and time course of locomotor swimming recovery that is seen in non-transplanted animals.

S27. Induction of Endogenous Reprogramming and Dedifferentiation of Adult Neurons in a Model of Spinal Cord Injury

Jeffery Plunkett, Angelo Milli, Sebastian Mariategui, Martin Oudega*

In contrast to the brain of mammals, fish and amphibians maintain multiple proliferative neurogenic and stem cell niches well into adult life. These niches provide a reservoir of cells that can be enabled for both central nervous system (CNS) growth and repair following injury. The pathway of neurogenesis in many model systems is often depicted as unidirectional by which stem progenitors differentiate into adult neurons. In a challenge to the unidirectional model are amphibians. In amphibians, CNS trauma causes reprogramming of fully differentiated cells (i.e., dedifferentiation) preceding their proliferation and (re-)differentiation and organization into new tissue. Our data demonstrate that adult zebrafish (Danio rerio) are also capable of reprogramming and dedifferentiating fully differentiated adult neuronal cells in response to injury. Following complete spinal cord injury (SCI) in adult zebrafish, we examined stem cell-related gene expression profiles in identified populations of differentiated brainstem neurons with an axon projecting into the spinal cord. Our data demonstrate that the neural stem cell progenitor cell markers sox 2, neuroD1 and oct 4 (Pou5f1) are differentially expressed in identified descending reticulospinal tract neurons during both acute and chronic phases post-SCI. Analysis of the cell proliferation marker PCNA indicated that these same neurons gained and lost the ability to divide during the acute and chronic phases respectively and eventually re-expressed the maturing neuronal marker HuC. These expression profiles suggest that the identified descending reticulospinal tract neurons reprogram, dedifferentiate and re-differentiate following SCI. We are currently examining axonal growth associated genes to correlate our findings to regenerative events seen typically in the spinal cord in adult teleost fish.

S28. Chronic Glucocorticoid Exposure Primes the Neuroinflammatory Response to Nerve Agent Sarin

Kimberly Kelly, Lindsay Michalovicz, James O'Callaghan*

Chronic exposure to the glucocorticoid corticosterone (CORT), at levels associated with high physiological stress, can exacerbate CNS proinflammatory responses to neurotoxic insults in animal models. Persistent sickness behavior, a prominent component of Gulf War (GW) Illness, is associated with neuroinflammation. Veterans of the 1991 GW were exposed to the stresses of war, being prophylactically treatmented with the reversible acetylcholinesterase (AChE) inhibitor pyridostigmine (PB), organophosphate pesticides chlorpyrifos (CPO) and dichlorvos (DDVP) and potentially the nerve agent sarin. We have previously shown CORT exacerbation of the neuroinflammatory response to CPO, DDVP, and the sarin surrogate diisopropyl fluorophosphate (DFP). Here, we confirm that sarin exposure also causes a neuroinflammatory response that is exacerbated by chronic CORT pretreatment. CORT (200 ug/mL in 0.6% EtOH) was given in the drinking water for 1 week prior to Sarin administration at an LD20 dose (0.1 mg/kg, s.c.) on day 8. Animals were euthanized at 6 hours and brains were dissected and then frozen for RNA and protein analysis. RNAseq analysis of cortex revealed 1535 genes that were significantly up-regulated in the CORT+Sarin group. Of these 211 were significantly greater than Sarin alone. These 211 genes were interrogated with DAVID to find GO terms which included cytokine production, MAP kinase phosphatase activity, and cytokine binding. Kegg pathways include: cytokine-cytokine receptor interaction, Jak-STAT signaling pathway, MAPK signaling pathway, and hematopoietic cell lineage. The neuroinflammatory response was further confirmed with elevated pSTAT3 protein by ELISA and elevated neuroinflammatory cytokines and chemokines mRNA(TNFα, IL6, CCL2, IL1β, LIF, and OSM) by qPCR. Together these findings confirm those we have previously shown with sarin surrogate, DFP and provide additional support for the hypothesis that GWI is a chronic, stressor-primed, neuroinflammatory condition potentially instigated by the combined exposures to stressors and irreversible AChE inhibitors.

S29. Damage to Thalamic Nucleus Reuniens Following Postnatal Alcohol Exposure Suggests Alterations to Prefrontal-Thalamo-Hippocampal Circuitry

Anna Klintsova, Zachary Gursky*

Individuals diagnosed with FASDs often display impairment in "executive function" (EF) behaviors. Many behaviors included under EF umbrella require coordination of the prefrontal cortex (PFC) and hippocampus (HPC). Recent non-human primate and rodent studies have demonstrated that the midline

thalamic nucleus reuniens (Re) is essential in coordinating PFC-HPC activity, as selective Re inactivation impairs PFC-HPC synchrony and behavioral performance on HPC- and PFC-dependent tasks.
In animal models, AE during the brain growth spurt targets structures, undergoing differentiation, layer formation and synaptogenesis, including HPC and PFC. Given Re critical role in coordinating PFC-HPC activity, we initially quantified immunofluorescently-labeled neurons (NeuN+) and cell nuclei (Hoechst33342-stained) in adult female Long-Evans rats exposed to 5.25 g/kg/day AE on postnatal days (PD) 4-9. We observed a significant loss of neurons in Re, but no change in non-neuronal cell number. All of these measures were unaffected in the neighboring rhomboid nucleus, suggesting specificity of this damage to Re within midline thalamus.
We next explored if there is a dose-dependent loss of neurons in the Re. Either "high-dose" 5.25 g/kg/day (BAC ≈340 mg/dL) or "moderate-dose" 3.00 g/kg/day (BAC ≈145 mg/dL) alcohol was delivered to male and female rats via intragastric intubation. The data suggest that both doses of alcohol produced significant NeuN+ cell loss in adulthood while neither dose resulted in altered number of microglia (immunofluorescent labeling of Iba1 protein). High-dose AE resulted in reduced Re volume, but moderate-dose AE did not alter Re volume. These data indicate that moderate-dose AE is sufficient to induce lasting damage in Re.
Taken together, our data suggest that Re is vulnerable to AE in development, resulting in significant neuron loss at both high and moderate doses. AE at this time in development does not appear to alter the number of glial cells (i.e., non-neuronal cells or microglia) throughout life.
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S30. Multiple Circadian Oscillators Mediate Food Anticipation in Rats

*Christian Petersen, Ralph Mistlberger**

Early in the 20th century, long before the word 'circadian' (~24h) was coined, Curt Richter (1922) reported that rats can anticipate a daily mealtime in an otherwise time free environment. Later studies showed that food anticipation exhibits formal properties of a clock-controlled rhythm entrained by periodic food access, including circadian 'limits to entrainment', i.e., anticipation is constrained to circadian feeding intervals (e.g., 24h but not 18h intervals). Despite this constraint, rats and mice can anticipate at least two daily meals. Conceptually, multiple meal anticipation could be mediated by a single clock used to discriminate and remember the circadian phase of each mealtime, or by multiple circadian clocks, each entrained to a unique mealtime. Despite

the parsimony of the single clock model, we provide evidence for multiple entrained oscillators. We find that rats can stably anticipate up to 4 daily meals, without light-dark cues or the master circadian clock in the suprachiasmatic nucleus. Remarkably, rats could anticipate 2 daily meals with different periodicities (one meal at 24h intervals, a second at 25 or 26h intervals). Importantly, during total food deprivation tests, both anticipation rhythms persisted, with a periodicity that matched the feeding interval to which they were synchronized. Math modeling supports the computational feasibility of a multiple entrained circadian oscillator model.

S31. Effects of Loss of SAP-97 and SAP-102 on Synaptic Plasticity During Motor Learning

Yixuan Pei, Richard Roth, Elena Ortega, Han Tan, Andrew Wu, Richard Huganir*

Learning and memory relies on synaptic plasticity mechanisms such as long-term potentiation and depression mediated through the up- or down-regulation of synaptic AMPA receptors (AMPAR). It has been shown that a group of scaffolding proteins within the membrane-associated guanylate kinase (MAGUK) family play a critical role in the regulation of AMPAR trafficking in the post-synapse. Here, we investigate how the local deletion of MAGUK scaffolding proteins, SAP-97 and SAP-102, in adult mice alter synaptic AMPAR levels in the motor cortex and how loss of these proteins affects motor learning. Therefore, we use viral expression of Cre recombinase in SAP-97 or SAP-102 conditional knock-out mice followed by behavioral analysis through motor training and molecular quantification through subcellular fractionation and immunoblotting to study effects on synaptic protein levels. Given the importance of synaptic AMPAR expression for proper learning and memory, our results show how scaffolding proteins regulate synaptic composition of AMPARs and their effect on motor learning in mice.

S32. AMPA Receptors Intracellular Trafficking: From ER to Plasma Membrane

*Françoise Coussen-Choquet**

AMPA receptors (AMPARs) mediate fast excitatory synaptic transmission in the central nervous system. Their abundance at the synapse is essential for the establishment and maintenance of synaptic function. Many studies characterized trafficking of AMPARs in spines at basal state or after induced plasticity. Their synaptic localization is dependent on a highly dynamic exocytosis, endocytosis and plasma membrane trafficking events. Our hypothesis is that synaptic localization of AMPARs is also regulated by their

earlier intracellular trafficking (ie: Endoplamic Reticulum (ER)-to-Golgi and Golgi-to-plasma membrane). However, AMPARs post-ER trafficking toward the plasma membrane still remains poorly understood.
Using a new biochemical tool combined with photonic live imaging, we controlled and followed the dynamic secretion of tagged AMPAR subunits in cultured rat hippocampal neurons. These approaches allowed us to characterize the AMPARs trafficking firstly from the ER to the Golgi apparatus and secondly from the Golgi to the plasma membrane.
We show that AMPARs require around 15-30 minutes to reach the Golgi apparatus passing through ER exit sites. After 45-60 minutes, both GluA1 and GluA2 reach the plasma membrane. They are localized at synapses after 2-4 hours. Furthermore, we were able to visualize the vesicular trafficking of homomeric GluA1 receptors. Since the scaffold protein SAP97 has been shown to be involved in the intracellular AMPARs traffic via its PDZ interaction with GluA1, we have studied its role in the GluA1 vesicular trafficking. We show that an abolishment of the PDZ interaction between GluA1 and SAP97 alters the GluA1 vesicular trafficking. We are studying how long term induced synaptic activity is able to regulate intracellular of GluA1 containing AMPAR.

M1. Female Rats Express a More Addictive Phenotype Than Male Rats During Intermittent-Access Heroin Self-Administration

Timothy O'Neal, Zackari Murphy, Garret Stuber, Susan Ferguson*

Opioid addiction is a chronic, relapsing disorder, characterized by bouts of drug-taking and drug-seeking. The current opioid epidemic is the leading cause of accidental death among adults and was responsible for more than 70,000 deaths in 2017. Although opioid overdose deaths have historically been more frequent in men, the death rate is rising faster in women due to a recent spike in heroin abuse. Addiction develops in part from disruptions within the cortico-basal ganglia circuit (C-BG), a network integral for learning, decision-making, and motivation. However, whether these changes contribute to sex differences in heroin addiction remains unknown. Here, we used a model of intermittent-access heroin self-administration in female and male Sprague-Dawley rats. Using behavioral metrics from self-administration, progressive ratio, extinction, and cue-induced reinstatement sessions, an overall addiction severity score was calculated for each rat. Female rats were found to express significantly greater heroin-seeking behaviors (responding during drug-unavailable periods, perseverative responding during extinction, responding during reinstatement) than male rats. Interestingly, however, female rats did not differ from male rats in heroin-taking behaviors (infusions per day, infusion rate across drug-available periods, motivation to self-administer heroin). Tissue was collected

following progressive ratio testing and extinction testing and processed for single cell-sequencing using 3-level scRNA-seq, or following reinstatement testing and processed for cFos immunohistochemistry. To complement these self-administration experiments, we are currently using conditioned place preference coupled with fiber photometry to investigate the role of the C-BG in heroin reward. Together, these experiments will add to our understanding of how key nuclei of the C-BG contribute to the development, expression, and maintenance of aberrant behaviors associated with heroin addiction.

M2. Exercise Prevents Incubation of Cocaine and Nicotine Craving and Multi-Triggered Relapse to Heroin

Marilyn Carroll, Lydia Fess, Ben Dougen, Jack Smethells, Natalie Zlebnik*

Background: Nicotine, cocaine, and heroin addiction have high rates of morbidity and mortality in the US. Most treatments have low success rate as with self-quit attempts. Hypothesis: treatment failures are due to incubated craving that builds over weeks to months after cessation and treatment ends, leading to relapse. Goal: to block incubation of craving and multi-triggered relapse (MTR) elicited by a wide range of stimuli.

A. Incubation of Craving

Methods: 1. Establish iv cocaine (0.4 mg/kg) self-administration, in female and male rats in operant chambers for 10 days of stable behavior.

2. Move rats to a different environment with access to a running wheel, (stationary wheel for controls) for 3 or 30 days.

3. Rats were returned to their operant chamber to test relapse responding with cues formerly available with cocaine. No drug was available.

Results: 1. Females ran at higher rates than males during the 3- and 30-day incubation periods.

2. Relapse responding (on drug lever) after wheel access was higher in the 30-day (vs. 3-day) groups indicating incubated craving.

3. Wheel-running blocked incubation of cocaine seeking at 30 days in both sexes. In males wheel-running also reduced craving after 3 days.

Conclusion: Exercise reduced incubation of cocaine seeking in females and males.

B. Multi-triggered Relapse

1. Establish i.v. heroin (0.015 mg/kg) self-administration in female and male rats for 10 stable days, then 21 days of extinction with a running- or stationary-wheel.

2. Test relapse responding with priming conditions (heroin, caffeine, yohimbine-stress, other drugs).

Results: 1. Females had more wheel revolutions than males.

2. Wheel running reduced lever responding in extinction (first 7 of 21 days).

3. Wheel-running reduced relapse cued by heroin, caffeine, stress, and females > males.
Conclusion: Exercise reduced MTR to heroin seeking in female and male rats.

M3. L-DOPA Decrease Oral Fentanyl Consumption

Ryan Farero, Janet Lee, Hope Willis, Paul Phillips*

Altered dopamine (DA) signaling is implicated in most contemporary theories of drug abuse. Both drugs of abuse and the cues that are repeatedly paired with drugs are capable of driving dopamine release in the nucleus accumbens core (NAcc). Work from our lab has shown attenuated dopamine release correlates with increased cocaine intake and demonstrated a causal relationship between dopamine transmission and cocaine consumption. More specifically, increased dopamine signaling during response-contingent drug cues in the NAcc decreases cocaine consumption. Given that the attenuated transient dopamine signals in the NAcc were specific to the drug-paired cue and not the substance itself, we hypothesize that dopaminergic transmission mediates drug satiation across multiple drugs of abuse. To test this hypothesis, the present work investigates pharmacological interventions during two self-administration behavioral assays in male and female rats. First, a two-bottle choice procedure was utilized in which animals were provided access to fentanyl or water. Administration of L-DOPA, the dopamine precursor, decreased fentanyl consumption ($p<0.05$), but had no effect on water consumed ($p>0.05$).Within the second task, an instrumental self-administration assay, animals responded at a nose-poke port eliciting delivery of fentanyl and an audiovisual stimulus. Administration of L-DOPA decreased the amount of active responding ($p<0.01$) and fentanyl consumed ($p<0.05$). To further investigate the brain loci mediating the observed effects L-DOPA was infused directly into the NAcc. The results of injections into the NAcc were surprising, as L-DOPA had a statistical trend to increase active responding ($p=0.0994$), but no change in fentanyl consumed was observed ($p>0.2$). Overall these results support the hypothesis that dopaminergic transmission mediates drug consumption. However, further studies will need to be performed to identify the brain loci responsible for the observed effects.

M4. Proestrus-Induced Decreases in Heroin Intake in Female Rats

Mark Smith, Sarah Ethridge, Abigail Gibson, Tallia Pearson, Huailin Zhang, Madison Marcus, Kenzie Potter, Andrea Robinson*

We previously reported that opioid intake decreases markedly during proestrus in normally cycling female rats. The purpose of this study was to determine if this effect could be artificially mimicked in ovariectomized rats

(Experiment 1) and to determine the endogenous hormones mediating this effect in intact rats (Experiment 2). Ovariectomized (Experiment 1) and intact (Experiment 2) female rats were surgically implanted with intravenous catheters and trained to self-administer heroin on a fixed ratio (FR1) schedule of reinforcement. In Experiment 1, ovariectomized rats were treated with estradiol (or vehicle) 22 hours before and progesterone (or vehicle) 1 hour before a test session to artificially mimic proestrus. In Experiment 2, the effects of estrogen and progesterone receptor antagonists on heroin intake were examined during proestrus in normally cycling rats. In Experiment 1, estradiol administered 22 hours before a test session significantly decreased heroin intake in ovariectomized rats; progesterone administered 1 hour before a test session did not alter heroin intake and did not enhance the effects of estradiol. In Experiment 2, the estrogen receptor antagonist raloxifene, but not the progesterone receptor antagonist mifepristone, significantly blocked proestrus-induced decreases in heroin intake. Collectively, these data indicate that proestrus-induced decreases in heroin intake are mediated by estradiol and not progesterone. These findings also suggest that the effects of ovarian hormones on heroin intake differ from that previously reported for other drugs (e.g., stimulants).

M5. Prior Cocaine Self-Administration Differentially Alters State Encoding in Distinct Dorsomedial Striatal Neuron Populations in Rats

Lauren Mueller*, Melissa Sharpe, Thomas Stalnaker, Andrew Wikenheiser, Geoffrey Schoenbaum

When the rules that govern our actions change, it is useful to learn about the new situation in a way that preserves old learning, building a library of associations that can be deployed as needed to match the current context. One way to achieve this is to compartmentalize learning about different contexts into distinct "states", each containing information relevant to a particular scenario. Using inputs from the orbitofrontal cortex, cell populations within the dorsomedial striatum (DMS) work together to maintain such state-specific associations. Since drugs of abuse are known to disrupt state-dependent behaviors and decision making, neural encoding of state within the DMS may be impaired by drug exposure.

Here, we assessed how a history of cocaine self-administration affected neural representations of state in medium spiny neurons (MSNs) and fast-spiking interneurons (FSIs), two of the major cell populations of the DMS. First, rats self-administered either sucrose or cocaine for two weeks. Several weeks later, single-unit activity was recorded while rats performed an odor-guided decision-making task comprised of two blocks of trials, or "states". In one state, odor cues were delivered to a central port and signaled the availability of a large reward

from one fluid well and a small reward from another well. In the second state, the odor-reward size contingencies were reversed. We found that cocaine-experienced rats were slower to adjust responding for large rewards following a state change as compared to sucrose controls. This behavioral change was accompanied by differences in state encoding by DMS MSNs and FSIs. Prior to odor onset, MSNs in the cocaine-experienced group exhibited decreased trial type classification accuracy, suggesting a loss of state representation relative to sucrose controls. However, following odor onset, FSIs in the cocaine group displayed increased trial type classification accuracy, demonstrating enhanced outcome representation. Together, these results indicate that DMS state encoding is disrupted by cocaine experience. These findings are consistent with a role for DMS cell populations in the regulation of behavioral flexibility and suggest that alterations in task encoding may contribute to the poor decision-making observed in individuals following exposure to drugs of abuse.

M6. Ventral Tegmental Area Glutamate Neurons Drive Reinforcement Absent of Dopamine Co-Release

Vivien Zell, Nick Hollon, Thomas Steinkellner, Shelley Warlow, Lauren Faget, Larry Zweifel, Xin Jin, Thomas Hnasko*

Like ventral tegmental area (VTA) dopamine (DA) neurons, we and others have shown that activity of VTA glutamate neurons can support positive reinforcement. However, a subset of VTA neurons co-release both DA and glutamate, and DA release may be responsible for behavioral reinforcement induced by activity of VTA glutamate neurons. To test this, we used optogenetics to stimulate VTA glutamate neurons in which tyrosine hydroxylase (TH), the rate-limiting enzyme in DA biosynthesis, was conditionally ablated using either a novel mouse model or a CRISPR-Cas9-based approach. These manipulations led to a loss of DA release evoked by VTA glutamate neuron stimulation in the nucleus accumbens (NAc), while glutamate neurotransmission remained intact. Despite the ablation of this DA signal, optogenetic activation of VTA glutamate cell bodies or terminal fibers in the NAc were both sufficient to support reinforcement in operant behavioral assays. These results strongly suggest that glutamate release from VTA terminals in the NAc is sufficient to promote reinforcement independent of DA co-release, establishing a new circuit mechanism by which VTA activity can influence reward-seeking behaviors.

M7. Perineuronal Net Degradation Alters Cocaine Reinstatement and Intrinsic Properties of Fast-Spiking Interneurons in the Rat Medial Prefrontal Cortex

Emily Jorgensen, Jake Aadland, Arianna Tourtellot, Tarver Boyce, Travis Brown*

Our laboratory is interested in the molecular underpinnings that mediate pervasive drug memories. Perineuronal nets (PNNs) are specialized extracellular matrix structures primarily surrounding parvalbumin-containing fast-spiking interneurons (FSI). Our research group previously published that removal of PNNs within the medial prefrontal cortex (PFC) attenuates cocaine-induced reinstatement of cocaine-conditioned place preference (cocaine-CPP) and increases the firing rate of pyramidal neurons within the prelimbic PFC. Our on-going research suggests that PNNs have a time-dependent effect on modulating firing activity of FSIs to influence pyramidal neuron activity. Rats underwent cocaine-CPP training and extinction. After meeting extinction criteria, rats were microinjected into the prelimbic PFC 3d prior to cocaine-induced reinstatement with either vehicle or chondroitinase ABC (ch-ABC) to degrade PNNs. This procedure has shown to previously reduce cocaine-CPP. 2 hr following reinstatement, brain slices containing the mPFC were prepared for whole-cell electrophysiological recordings. PNN degradation resulted in an attenuation in the number of current-induced action potentials (APs) (vehicle: 99.0±7.31; ch-ABC: 53.33±1.43). In addition, we found significant changes in both the halfwidth and afterhyperpolarization potential (AHP) of APs in FSIs following ch-ABC treatment when compared to controls. Differences in these specific intrinsic properties suggest that there could be alterations in the currents responsible for the AHP and halfwidth. Current experiments are investigating the role of slow conductance potassium channels in these intrinsic differences. Furthermore, we are examining if PNN degradation alone affects intrinsic excitability and synaptic transmission within the mPFC. Through this work, we aim to further identify how PNNs are altering intrinsic and synaptic transmission following cocaine-associated learning, which contributes to persistent drug craving.

M8. Nucleus Accumbens Cholinergic Interneurons Drive Dopamine Release During Motivated Approach

Joshua Berke, Ali Mohebi*

The mesolimbic dopamine pathway is critically involved in both learning from past rewards, and motivation to work for future rewards. How dopamine achieves these distinct functions is not fully known. Learning is thought to involve bursts of dopamine cell spikes encoding prediction errors. Separately, many groups including ours have observed ramps in accumbens dopamine release, that accompany motivated approach behaviors and may encode

reward expectation (value; Mohebi et al. Nature 2019; Hamid et al. Nat Neuro 2016). Surprisingly, value-related changes in accumbens dopamine release occur without any change in spiking of VTA dopamine cells. We hypothesized that motivational functions involve local regulation of release via receptors on dopamine terminals. A candidate mechanism involves striatal cholinergic interneurons (CINs): in brain slices, CIN stimulation evokes dopamine release via nicotinic receptors.
We first established that this mechanism operates in awake, freely-moving rats. We expressed ChR2 selectively in accumbens CINs, and stimulated these neurons while monitoring dopamine release through the same optic fiber using the red-shifted dopamine sensor RdLight1 (created by T.Patriachi, L.Tian). We observed a robust increase in dopamine, that scaled with the duration and intensity of stimulation (n=4 fibers, 2 rats). Next, we examined whether the natural activity dynamics of CINs can account for value-related dopamine release. Using fiber photometry and the calcium indicator GCaMP6f we observed rapid increases in CIN activity during motivated approach (n=8 fibers, 5 rats), mirroring the dopamine dynamics that cannot be accounted for by VTA dopamine cell firing. These results support the hypothesis that motivation-related changes in accumbens dopamine release are locally controlled by CINs.

M9. Delineating the Molecular Architecture of the Dopaminergic Presynapse by Super-Resolution Microscopy

Ulrik Gether, Matthew Lycas, Jonatan Støier, Søren Heide Jørgensen, Daryl Guthrie, Luke Lavis, Andreas Sørensen, Amy Newman, Freja Herborg*

The dopaminergic presynapse consists of a unique repertoire of molecular components of which some are unique to dopaminergic or monoaminergic neurons while others make up generalized synaptic features. Indeed, processes in the presynapse that govern dopamine (DA) storage, release and clearance can modulate DA's sphere of influence in target structures and may constitute paths upon which dopaminergic dysfunction in disease converges into distinct patterns of synaptic deficits. Single-molecule super-resolution microscopy techniques, such as direct stochastic optical reconstruction microscopy (dSTORM), has brought the advantages of fluorescence microscopy together with a resolving power approaching that of EM, making super-resolution an unprecedented tool for discovering structural correlates for synaptic function. Recently, we have performed comprehensive super-resolution analyses of the dopamine transporter. Our studies revealed how DAT moves in and out of cholesterol-enriched nanodomain in presynaptic release sites of dopaminergic neurons in a manner dependent on neuronal activity. Brief stimulation of NMDA receptors in dopaminergic neurons, for example, caused Ca2+-dependent dispersing of DAT nanoclusters but not of other key membrane

proteins in the DAT presynapse. In contrast, brief stimulation with the amphetamine, did not affect DAT distribution but elicited surprising changes in the nanodomain distribution of other molecular components belonging to the synaptic release machinery. The data demonstrate how application of super-resolution microscopy in quantitative manner can visualize dynamic architectural alterations in the presynapse that might be of critical importance not only for synaptic function but also for drug responses and even diseased states within the dopaminergic system.

M10. Extended-Release Injectable Naltrexone Before vs. After Reentry for Opioid Addicted Prisoners

*George Woody**

Background: Correctional facilities have a high prevalence of persons with opioid use disorders. Usual treatment in the U.S. is clonidine detoxification and referral to treatment at reentry. Few offer evidence-based medicine for opioid use disorders and relapse with overdose death after reentry is common. Extended-release injectable naltrexone (XR-NTX) might improve outcomes, particularly if given before reentry. Methods: Consenting, detoxified, opioid addicted prisoners in the Philadelphia county jail were randomized to receive XR-NTX before reentry (BR) or after reentry (AR) and offered monthly XR-NTX, weekly counseling, and weekly to monthly outcome assessments to month 6. PRIMARY Outcome: relapse during the first 3 months after reentry determined by 10 or more days of self-reported opioid use, withdrawal, and/or two or more opioid positive urine tests within a 4-week period. Secondary outcomes: XR-NTX doses received, overdoses, overdoses and overdose deaths, reincarceration. Results: 422 prisoners expressed interest over 18 months of recruitment, met admission criteria and consented, 86 were released to outpatient treatment. Non-relapse by month 3was 39.5% in BR vs. 25% in AR (p=0.20). BR patients remained in treatment longer and received more XR-NTX than AR patients due to higher rates of receipt of the first (100%) and return for the second injection (50%). 2BR patients had non-fatal ODs vs 6 AR patients. There were 4 OD deaths, 3 in AR, two within days of reentry. All ODs were in patients that never started XR-NTX or started and dropped out. 9 BR and 10 AR patients were receiving XR-NTX at month 4. Fifty were re-incarcerated within the 28 months of study recruitment, treatment and follow up, 28 in BR, 22 in AR (p=0.01). Conclusions: Some opioid addicted prisoners are interested in XR-NTX and much more likely to receive it if administered before reentry. Starting it BR did not reduce relapse over 3 months after reentry. The apparent OD protection associated with XR-NTX adherence is consistent with its pharmacology and data from other recent studies. Limitations: High levels of dropout, particularly in AR patients, with reliance on self-reports for the primary and most secondary outcomes.

M11. GluA1 Expression in Cortical-Accumbal Circuitry of Differentially Reared Rats

Margaret Gill, Adam Lundquist, Frank Pignone, Dylan Laux, Alexa Zimbelman, Michael Stefanik*

Early environmental experience impacts susceptibility to drug abuse later in life. Rearing rats in enriched (EC) or impoverished (IC) conditions results in rearing-induced neurobiological, neurochemical, and behavioral changes. In particular, rats reared in an enriched condition (EC) following weaning exhibit a protective effect, as EC rats are less reactant to the rewarding properties of psychostimulant drugs at low doses, and self-administer less drug than rats reared in an impoverished condition. Previous work implicates nucleus accumbens (NA) GluA1 in cocaine self-administration and reinstatement, and prelimbic cortex GluA1 in extinction. Based on this previous research, and work in our own lab showing attenuated drug seeking behavior in IC rats infused with an AMPA positive allosteric modulator into the infralimbic cortex (IL), the current study sought to determine if GluA1 expression is differentially altered in the prelimbic cortex (PL), IL and NA of EC and IC rats, following cue-induced reinstatement. Rats were reared in either EC or IC environments for 30 days, and then trained to self-administer cocaine using a 2-hr self-administration model (FR1; 4.0 mg/mL cocaine dose). Following extinction, rats underwent cue-induced reinstatement, and brains were immediately extracted from the rats. Tissue was processed and immunoblotting was used to quantify GluA1 protein levels in the NA, PL, and IL. Immunoblotting results reveal that EC rats display greater GluA1 expression in the PL compared to IC rats, while there are no differences in GluA1 expression in the IL and NA. This suggests that AMPA receptors levels in cortical areas are altered by differential rearing, and this may be a mechanism by which EC rats are protected from drug-taking behavior.

M12. Validation of Fos-mRFP Rats to Map Neuronal Ensembles Underlying Reward-Related Behaviors

Katherine Savell, Rajtarun Madangopal, Leslie Whitaker, Jae Choi, Elise Van Leer, Sophia Weber, Veronica Lennon, Megan Brenner, Lauren Komer, F. Javier Rubio, Bruce Hope*

Learned associations are thought to be encoded by sparsely distributed populations of activated neurons called 'neuronal ensembles'. Sustained neuronal activity triggers cellular signaling cascades which result in the induction of immediate early genes (e.g. Fos, Arc, Egr1) that are used as markers to identify neuronal ensembles. Fos-expressing ensembles have recently been shown to mediate a number of reward-related behaviors. Rats are commonly used to model complex behavioral and cognitive processes and are often viewed to have more relevance as a model for human disease, but limited transgenics exist due to difficulties in genetic manipulation. Here, we

characterize reward-related regions of a previously generated transgenic rat line that expresses a monomeric red fluorescent protein (mRFP) under the control of the Fos promoter to label Fos-expressing ensemble neurons. We tracked the time-course of Fos and mRFP expression in the infralimbic and prelimbic subregions of the prefrontal cortex after novel context exposure. The overlap between mRFP- and Fos-positive cells was consistently high and the proportion of mRFP-only cells consistently low across all timepoints investigated. Our results indicate that the spatiotemporal expression of mRFP reliably matches that of Fos in this transgenic rat line i.e. mRFP expression is specific to neurons that express Fos. Ongoing work aims to validate transcriptional dynamics of Fos and mRFP expression through FACS and the role of cellular signaling cascades in vitro. The Fos-mRFP transgenic rat allows longitudinal investigation of Fos-expressing neurons in vivo and can be used in conjunction with green fluorescence-based indicators to investigate properties of neuronal ensembles in reward-relevant behaviors.

M13. Reward Expectation Differentially Drives Dopaminergic Responses Across Striatal Sub-Regions

Christopher Donahue*, Benjamin Margoin, Jacob Nadel, Aphroditi Mamaligas, Anatol Kreitzer

Dopamine is thought to play a central role in learning and motivation through its influence on striatal circuitry. Recent work has demonstrated that striatal dopamine signaling is much more diverse that previously thought, with movement and reward signals differing dramatically across different striatal sub-regions. However, the functional role of these heterogeneous responses have not been characterized in detail. To investigate this, we trained mice to perform two complementary tasks in which we systematically manipulated the amount of effort required to obtain reward. In the first task (fixed ratio), the number of movements required for reward delivery was manipulated in blocks so that the amount of effort required was predictable. In the second task (variable ratio), the number of movements were randomized and could not be predicted. We found that movements became successively faster as the animals progressed through the nose-poke sequence only in the fixed ratio task, demonstrating that knowledge about reward proximity invigorated their upcoming movements. We expressed a dopamine sensor (dLight 1.1) bilaterally across three different striatal sub-regions (dorsomedial, dorsolateral, and ventral striatum) and recorded fluorescence while animals performed each task. The magnitude of movement-evoked dopamine release systematically increased as animals got closer to reward in all sub-regions in the fixed ratio task, but not in the variable ratio task. Next, we compared activity across hemispheres and found that both movement and reward signaling were more lateralized in the dorsomedial striatum compared to other sub-regions. Together, our results demonstrate

that striatal dopamine is robustly modulated by reward expectation, and that dopamine in the dorsomedial striatum may play a unique role in directing action towards locations that are more likely to lead to reward.

M14. Investigating the Role of TrkB in Value-Based Decision Making

Ellen Woon, Ari Peluso, Shannon Gourley*

Value-based decision making, referring to selecting actions with the expectation they will be rewarded with valued outcomes, relies on the medial orbitofrontal cortex (mOFC). One molecular candidate that likely sustains value-based decision-making is Brain-derived Neurotrophic Factor (BDNF). Given that BDNF is subject to anterograde and retrograde transport, however, where (and when) BDNF binding is necessary for optimal decision making remains unclear. Here, we administered an antagonist against the high-affinity BDNF receptor, tyrosine/tropomyosin receptor kinase B (TrkB), during the encoding or retrieval of new memories regarding food value. Inhibiting TrkB activity during the encoding, but not the retrieval, of new memory regarding food value impaired value-based action selection. Then, to determine where TrkB activity was necessary for value-based decision making, we overexpressed an inactive isoform of TrkB, TrkB.t1, in the mOFC or basolateral amygdala (BLA), which shares connections with the mOFC. TrkB.t1 overexpression in both regions impeded optimal response selection, but in dissociable manners. Specifically, TrkB activity in the mOFC is involved in value-based action when action outcomes are not observable and must be inferred. Meanwhile, TrkB activity in the BLA is necessary for value-based action regardless of whether outcomes are observable or action selection requires inference and prediction about the future. These patterns suggest that neurotrophin activity in the BLA is necessary for optimal action selection strategies, potentially by conveying outcome value information to other structures, such as the mOFC, with more specialized functions.

M15. Prefrontal Neuronal Encoding of Threat-Related Stimuli Across the Estrous Cycle

Marieke Gilmartin, Matthew Herbst, Matthew LaViola, Robert Twining*

The association of a neutral conditional stimulus (CS) and aversive footshock unconditional stimulus (UCS) that are separated in time, as in trace fear conditioning, requires activity in the prelimbic area (PL) of the medial prefrontal cortex. We have previously shown that a subset of PL cells shows sustained firing in response to the CS and that optogenetic silencing of prefrontal activity during the trace interval between the cue and shock prevents learning (Gilmartin & McEchron, 2005; Gilmartin et al., 2013). Recently, we

have uncovered sex differences in the prefrontal cortical contribution to trace conditioning (Kirry et al., 2018; 2019). In one study, the estrous cycle gated the memory-impairing effects of a muscarinic antagonist in the PL (Kirry et al., 2019), which suggested that circulating ovarian hormones may modulate prefrontal encoding during aversive learning. Here we recorded neuronal activity in the medial prefrontal cortex during the acquisition and extinction of trace fear conditioning. The estrous cycle of female Long-Evans rats was tracked for two cycles and then half of the rats started training on the day of proestrus and the other half started training on the day of metestrus. Training occurred over two days and testing in a shifted context occurred when the rats returned to their initial training cycle stage. Initial results (n = 6/group) have revealed similar sustained activation to the CS but divergent encoding of the UCS during day 1 of training. Proestrus females exhibited a robust increase in firing in response to the UCS, and metestrus females exhibited a modest response. Neuronal encoding on day 2 of training and subsequent conditional fear to the cue and context at test was similar between groups. Follow-up experiments will determine whether these divergent patterns of PL encoding of the UCS mediate cycle differences in cued fear retention after only one day of training, that can be overcome with additional training. These findings will reveal how prefrontal encoding of threat-related stimuli does and does not change across the estrous cycle, shedding light on how neuromodulation of prefrontal activity differentially affects the formation of fear memories between sexes and across the estrous cycle.

M16. Temporal Dynamics of Spatial Information Encoding Within Retrosplenial Cortex

Megha Sehgal*, Sunaina Martin, Asli Peckan, Daniel Aharoni, Shan Huang, Ayal Lavi, Alcino Silva

Memories are dynamic in nature and a cohesive representation of the world requires memories to be linked with other related memories. Our laboratory has recently demonstrated that the overlap between the hippocampal CA1 ensembles encoding two contextual memories acquired close in time mediates memory linking, whereby the recall of one memory can lead to the recall of another memory (Cai et al. 2016). Retrosplenial cortex or RSC is another brain structure that is critical for contextual learning and memory. It is unclear whether memory linking is a specific property of CA1 ensembles or whether other brain regions involved in contextual processing also display this pattern of neuronal overlap between ensembles encoding memories acquired close in time. We addressed this question by investigating the overlap in RSC neuronal ensembles encoding contextual memories at varying time intervals. Using head-mounted fluorescent microscopes (miniscopes), we imaged GCaMP6f-meadiated calcium dynamics in retrosplenial cortical neurons while the mice explored distinct contexts. We found greater overlap in the neuronal

ensemble activated in response to two distinct contexts when the contexts were explored 5-hours vs. 7-days apart. These data suggest that the RSC could mediate temporal memory linking by recruiting a shared neuronal ensemble for memories encoded within a day. Furthermore, to understand whether such ensemble overlap was driven by neurons encoding spatial information, we performed linear track experiments where RSC calcium transients were imaged using miniscopes. We found that a subset of RSC cells (~35%) displayed place cell like dynamics. Furthermore, the same cells could be followed over repeated linear track sessions. These cells displayed stable firing patterns indicating retention of spatial information over days. Interestingly, the reactivation of RSC place cells over subsequent linear track sessions was similar to that of RSC non-place cells indicating that RSC place cells follow similar temporal dynamics as the non-place cells. All together our data indicate that co-allocation of neuronal ensembles encoding temporally proximate contextual memories may be a general mechanism of memory linking across the brain regions that process spatial and contextual information.

M17. Making Sense of Computational Psychiatry

Helmut Strey, Lilianne Mujica-Parodi*

In clinical neuroscience we often speak of constructing "models." Here we try to make sense of what such a claim might mean, starting with the most fundamental question: "What is (and isn't) a model?". We then discuss, in a concrete measurable sense, what it means for a model to be useful. In so doing, we first identify the added value that a computational model can provide, in the context of accuracy and power. We then present the limitations of standard statistical methods and provide suggestions for how we can expand the explanatory power of our analyses. Finally, we address the problem of model building—suggesting ways in which generative models can escape the potential for cognitive biases imposed by classical hypothesis-driven research, exploiting deep systems-level information contained within neuroimaging data to advance our understanding of psychiatric neuroscience.

To illustrate our approach, we will present a stochastical model for fMRI measurements of the human resting state and compare it quantitatively to other theoretical models.

M18. Neural Precursor Cell Derived Brain-Like Tissue Induces the Formation of Long-Range Connections in the Adult Brain

Gretchen Greene, Nikorn Pothayee, Dragan Maric, Stephen Dodd, Alan Koretsky*

Neurodegeneration is a hallmark of many neurological disorders, stroke, and traumatic brain injury. However, the central nervous system (CNS) generally lacks the ability to regenerate damaged neurons, and therefore treatments that repair and promote neuronal growth are highly desirable. Neural stem cell transplantation has potential to replace neuronal tissue lost due to injury or disease, yet current research has not evaluated the ability for long distance axonal ingrowth originating from the host brain projecting to graft, which may be critical for functional recovery and repair. Previously we have shown that early-stage neural precursor cells (NPCs) implanted in the cerebrospinal fluid of adult rats develop into a brain-like tissue (BLT) that is integrated with the host brain. The NPCs differentiate into neurons and astrocytes forming a tissue growth that is vascularized by the host. Additionally, host GABAergic interneurons and microglia migrate into the BLT and we find oligodendrocytes originating from both the host brain and the transplanted NPCs. In this study, we implanted NPCs near the subventricular zone of 3 week and 4 month old host rats. The NPCs developed into an integrated brain-like tissue in both 3 week and 4 month old host brains and neurons derived from the implanted NPCs sent long range axonal projections along the rostral-migratory stream into the host olfactory bulb. Strikingly, the host brain developed long-distance axons projecting into the BLT. Through tracing with retrograde AAV and Fluorogold, we have found that the host axons innervating the new tissue growth originate in the prefrontal cortex. Additionally, we see that neurons derived from the transplanted precursor cells project back to the prefrontal cortex suggesting a level of reciprocal connectivity. This demonstrates the ability of transplanted NPCs to integrate with the mature brain circuitry. The potential of NPCs to form integrated neuronal tissue and induce bidirectional long-range connectivity may have implications for CNS regenerative medicine and open up questions about axonal plasticity in post-critical period brain development.

M19. Sex Differences in Body Composition but Not Neuromuscular Function Following Long-Term, Doxycycline-Induced Reduction in Circulating Levels of Myostatin in Mice

Sonsoles de Lacalle, Dallin Tavoian, Sophia Mort, W. David Arnold*

Age-related declines in muscle function result from changes in muscle structure and contractile properties, as well as from neural adaptations. Blocking myostatin (MSTN) to drive muscle growth is one potential therapeutic

approach. While the effects of myostatin depletion on muscle characteristics are well established, we have very little understanding of its effects on the neural system. Here we assess the effects of long-term, post-developmental myostatin reduction on motor unit characteristics and body composition in aging mice. We used male and female mice containing a tetracycline(DOX)-inducible system to delete MSTN in skeletal muscle. Starting at 12 months of age, half of the mice were administered DOX through their chow for 1 year. During that time, we measured food intake, body composition, and hindlimb electromyographic responses.
DOX-induced MSTN reduction had no effect on motor unit properties for either sex, but significant age-dependent declines in motor unit number occurred in all mice. Treatment with DOX induced different changes in body composition between sexes. All female mice increased in total, lean and fat mass, but DOX-treated female mice experienced a significantly larger increase in lean mass than controls. All male mice also increased total and lean mass, but administration of DOX had no effect. Additionally, DOX-treated male mice maintained their fat mass at baseline levels, while the control group experienced a significant increase from baseline and compared to the DOX treated group. Our results show that long-term administration of DOX results in body composition adaptations that are distinctive between male and female mice, and that the effects of MSTN reduction are most pronounced during the first three months of treatment. We also report that age-related changes in motor unit number are not offset by reduced MSTN levels, despite increased lean mass exhibited by female mice.

M20. The Role of Inflammation Markers in Functional Cortical Activation Deficits During Manual Tasks in Postmenopausal Women With Type II Diabetes

Stacey Gorniak, Arturo Hernandez, Luca Pollonini*

The overall aim of this project was to evaluate the relationship among outcomes in manual sensorimotor behavior, cortical activation, and health state markers in postmenopausal females with Type II Diabetes (DM). Our recent studies have shown that adults with DM experience declines manual sensorimotor function that are not associated with a diagnosis of diabetic peripheral neuropathy (DPN); however, it is not clear if cortical deficits are responsible. Currently, no specific consistent structural deficits have been identified as a cause to motor deficits in persons with DM. The reported behavioral deficits may be exacerbated in older adult females with DM, who are at the highest risk of cardiovascular decline, as DM is considered a cardiovascular disease. Twenty-one (21) community-dwelling DM patients (age = 65 ± 6 years, A1c = 7.5 ± 1.1) and twenty-one (21) age- and sex-matched healthy controls (age = 66 ± 6 years, A1c = 5.4 ± 0.3) were recruited and evaluated in this

cross-sectional study. Tactile detection and motor performance were evaluated while study participants donned cortical functional near-infrared spectroscopy devices (fNIRS) in one testing session. Tactile detection was evaluated via fingertip vibration; motor performance was evaluated by isometric pinch force production at two force levels using the thumb and index finger of the right hand. Bilateral cortical regions of interest (ROIs) included: PFC, SMA, M1, S1, and Brodmann area 40. Health state, metabolic, and menopausal status data were collected. No differences in tactile function were found between the two groups. No between group ROI activation differences were found in the tactile stimulation task. Deficits in sensory function and fine motor performance were found in the DM group ($p < 0.01$). Reduced HbO responses were found across all ROIs in the DM group ($p < 0.05$) during performance of the lower force level motor task. Group-based ROI activations did not show significant differences during the high force production task. Reduced HbO was associated with: (a) worsened motor function, and (2) worsened health state indices. These data are the first to indicate functional cortical deficits in postmenopausal females with DM. This suggests a potential combination of central deficits and inflammation leading to functional declines with aging and DM.

M21. Repeated Mild Traumatic Brain Injury Impairs the Functional Integrity of the Locus Coeruleus-Noradrenergic System

Barry Waterhouse, Alexis Foschini, Leah Horvat, Doug Fox, James Grininas, David Devilbiss*

Mild traumatic brain injury (mTBI) affects approximately 1.7-3.8 million Americans each year. TBI is a complex pathophysiological process resulting in behavioral and cognitive deficits including impaired arousal, attention, decision-making, and other executive functions. Although symptoms generally resolve within three months after a single insult, repetitive mild injuries may produce cumulative effects, increase the susceptibility for further mTBI, and increase the likelihood of long-term cognitive deficits. Catecholamine systems, including the locus coeruleus (LC) -norepinephrine (NE) pathway, are critical regulators of the higher executive processes affected by TBI. Impaired LC-NE function is implicated in the pathogenesis of the cognitive and neuropsychiatric symptoms following moderate to severe TBI. Yet, the effects of mild TBI and repetitive TBI on catecholamine system function are poorly understood. Methylphenidate (MPH) and other psychostimulants are used to improve normal executive processes and to treat attention deficit hyperactivity disorder (ADHD). However, limited and inconsistent findings exist on the efficacy of MPH for treating the cognitive impairments following mild TBI due to small sample sizes, poor patient stratification, and limited dose ranges. The objectives of the current study were to determine the extent of LC-NE

functional impairments following repetitive mild TBI and to assess its response to a challenge dose of MPH. We found a reduction in dopamine-β-hydroxylase (DBH) and norepinephrine transporter (NET) immunoreactivity within the prefrontal regions of the rat brain following repetitive mild TBI. Additionally, baseline LC neuron discharge patterns, NE efflux within the prefrontal cortex, and the response of the LC-NE system to the MPH challenge were significantly altered after repetitive mild TBI. These findings provide critical insight into the sensitivity of catecholamine fibers to repeated mild TBI and support for the role of noradrenergic fiber injury in the cognitive deficits resulting from repeated injury.

M22. Perampanel Treatment of Benzodiazepine-Refractory Status Epilepticus

*Jerome Niquet, Ireri Franco Estrada, Claude Wasterlain**

Objective: To assess the effectiveness of perampanel, a specific antagonist for AMPA-type glutamate receptors, as a second-line treatment of benzodiazepine-unresponsive Status Epilepticus (SE).
Background: SE responds poorly to benzodiazepines, especially when treatment is delayed. Experimental data show that SE causes an early maladaptive internalization of synaptic GABAA receptors, which may explain benzodiazepine pharmacoresistance, along with a migration of NMDA and AMPA receptors (AMPAR) towards synapses, increasing glutamatergic excitation. Topiramate, an AMPAR antagonist, is often effective in refractory SE, and the stronger AMPAR antagonist perampanel deserves evaluation in the treatment of SE.
Design/Methods: SE was induced in adult male Sprague-Dawley rats by high-dose lithium/pilocarpine, and EEG/video was recorded for 18 hrs. Midazolam (1 mg/kg; ip) was injected 40 min after SE onset. Perampanel (0.5, 1 or 2 mg/kg, ip) or valproate (270 mg/kg) was injected 20 min following midazolam if SE continued.
Results: During the first hour following treatment with perampanel 2 mg/kg (−84 ± 314; $p<0.0001$) or 1 mg/kg (170 ± 410; $p<0.01$), but not valproate 270 mg/kg (453 ± 393), EEG power was decreased compared to midazolam alone (671 ± 208). Perampanel 2 mg/kg (median = -514; interquartile range: -1072 to -73; $p<0.001$) or 1 mg/kg (207; -675 to 758; $p<0.05$), but not valproate 270 mg/kg (1027; 396 to 3346), also significantly reduced the EEG power integral over the 6 h posttreatment when compared to midazolam alone (2407; 1557 to 3813). In addition, after perampanel 2 mg/kg the time needed for EEG amplitude to decline to twice the pre-seizure baseline (median = 11 min; interquartile range: 6 min – 31 min), was reduced compared to midazolam (42 min; 33-77 min); $p < 0.05$), suggesting earlier SE termination.

Conclusions: Perampanel is potent in stopping midazolam-refractory SE even when given 60 min following SE onset in this animal model of severe SE.

M23. Projectile Concussive Impact as a Preclinical Model for Traumatic Brain Injury

Lindsay Michalovicz, Kimberly Kelly, James O'Callaghan*

Traumatic brain injury (TBI) is as a major cause of death and disability experienced by nearly 3 million people per year. These injuries can be experienced in any environment, e.g. work or home, and can result from falls, vehicular accidents, or from being struck by or against an object. While TBIs can be severe and/or fatal, the majority of injuries are considered to be mild. However, even mild TBI has the potential to have long-lasting neurological effects including headaches, cognitive or memory impairments, mood dysfunction, and fatigue. By using animal models of TBI, we can investigate the underlying pathophysiology that can lead to neurological dysfunction in the absence of serious trauma (i.e. penetrating injuries). Here, we used a projectile concussive impact (PCI) model of mild TBI developed at Walter Reed Army Institute of Research, where a ball bearing is propelled at the head by air pressure. While several studies using PCI have employed a helmet to mitigate direct damage from impact, we needed to utilize a non-helmeted model of PCI-induced TBI in order to evaluate the protective nature of different helmet materials for the mitigation of work-related TBI. Adult male Sprague-Dawley rats were used to evaluate neurobehavioral, neuroinflammatory and neural damage end points up to 72 hours following TBI using different types of ball bearing. Animals that received TBI using either aluminum or steel ball bearings took approximately 1.7 and 7.3 times longer to recover from anesthesia compared to sham controls. Moreover, while rats impacted with aluminum were behaviorally normal even 1 hour following TBI, those impacted with the steel ball bearing had an impaired neurobehavioral score for up to 24 hours post-TBI which correlated with the presence of subdural hematoma and significantly higher markers of neuroinflammation. This non-helmeted variation of the PCI model is capable of producing a TBI which can be used for the future evaluation of helmet materials.

M24. CaMKII Versus DAPK1 Binding to GluN2B in Ischemic Neuronal Cell Death After Resuscitation From Cardiac Arrest

Olivia Buonarati, Sarah Cook, Dayton Goodell, Nicholas Chalmers, Nicole Rumian, Jonathan Tullis, Susana Restrepo, Steven Coultrap, Nidia Quillinan, Paco Herson, Ulli Bayer*

DAPK1 binding to GluN2B-containing NMDA receptors was prominently reported to mediate ischemic cell death in vivo. DAPK1 and CaMKII bind to the same GluN2B region, and their binding is mutually exclusive. Here, we show that mutating the binding region on GluN2B (L1298A/R1300Q) protected against neuronal cell death induced by cardiac arrest followed by resuscitation. Importantly, the GluN2B mutation selectively abolished only CaMKII but not DAPK1 binding. During ischemic or excitotoxic insults, CaMKII further accumulated at excitatory synapses, and this accumulation was mediated by GluN2B binding. Interestingly, extra-synaptic GluN2B decreased after ischemia, but its relative association with DAPK1 increased. Thus, ischemic neuronal death requires CaMKII binding to synaptic GluN2B, whereas any potential role for DAPK1 binding is restricted to a different, likely extra-synaptic population of GluN2B.

M25. Data Archive for the BRAIN Initiative (DABI)

*Rachael Garner, Nader Pouratian, Arthur Toga, Dominique Duncan**

In the field of invasive neurophysiology, studies are costly and prohibitive, as patients are not often willing to undergo neurosurgery for experimental devices or elective experiments, so data sharing is of great importance. For example, data sharing may allow individual researchers to generate statistical power to prove an experimental device is safe and effective and identify candidate subjects, target sites, and stimulation parameters.

Data Archive for the BRAIN Initiative (DABI) fills this scientific need by providing a centralized database for human invasive neurophysiology data – clinical, imaging, pathology, demographics, behavioral, and electrophysiology. The archive ingests, harmonizes, aggregates, stores, visualizes, and disseminates multimodal data (Fig.1). DABI allows data providers to organize and analyze data in one platform and also encourages multi-site investigations. Investigators can build multi-site cohorts based on filters, including gender, diagnosis, age, recording location, and data modalities available (Fig.2). Data trends and correlations can then be calculated in DABI without downloading raw data. Integrated software and analytics include image visualization, quality control, LONI Pipeline, Jupyter, R Analysis and Visualization of intracranial EEG Data (RAVE), and a variety of statistical tests.

Investigators maintain complete ownership and control of their data. Unaffiliated users must be granted access from PIs to download raw data or conduct analysis using DABI's built-in analytics.
DABI is a platform of networked and centralized web-accessible data archives to capture, store, and curate invasive human neurophysiological data and make them broadly available and accessible to the scientific community for furthering neuroscience research. Moreover, DABI also alleviates the burden on investigators to organize and ingest their data by harmonizing and storing the vast array of data collected in invasive human recording studies.

M26. Characterization of a Novel Allelic Variant of the Human Dopamine D2 Receptor

Kim Neve, Dayana Rodriguez, Michelle Kielhold, Brooks Robinson, Alec Condon, Naeem Asad, Timothy Dore, John Williams*

A novel DRD2 variant has been identified encoding a D2 receptor (D2-Mut) with an amino acid change in the third cytoplasmic loop. When transiently expressed in HEK293 cells, the D2-Mut receptor density is about 35-40% of D2-WT. We assessed arrestin recruitment, G protein activation, and stimulation of cyclic AMP accumulation by D2-Mut. Maximal arrestin recruitment by D2-Mut was ~half that of D2-WT, even when expressed at similar levels, and was characterized by a faster decay, compared to D2-WT, and by almost complete dependence on overexpression of GRK2. In contrast, quinpirole dose-response curves for activation of Gαi by D2-Mut were left-shifted 5- to 7-fold compared to D2-WT, indicative of more efficient G protein activation. Basal activation of G protein in HEK293 cells expressing D2-Mut was increased by 30% of the maximal response to D2-WT, consistent with enhanced constitutive (unliganded) activity. We also observed left-shifted dose-response curves and increased basal activity for inhibition of forskolin-stimulated cyclic AMP accumulation by D2-Mut. After AAV-mediated expression in dopamine neurons of D2 autoreceptor knockout mice, both variants mediated synaptic currents in response to release of endogenous dopamine, whether spontaneous or elicited by electrical stimulation, and in response to iontophoretic dopamine, but time-to-peak was slower and peak half-width was greater for D2-Mut. Uncaging of photoactivated sulpiride (CyHQ-sulpiride) produced an apparent inward current of about 10 pA in cells expressing D2-WT, consistent with inhibition of a tonic GIRK current. CyHQ-sulpiride photolysis produced a much larger inhibition of 60-70 pA in cells expressing D2-Mut. To determine whether the sulpiride response reflected inverse agonism of constitutive activity or antagonism of endogenous dopamine, slices were treated with reserpine 1 hr prior to recording. Reserpine-induced dopamine depletion abolished the response to sulpiride in cells expressing D2-WT and greatly decreased the response in cells expressing D2-Mut, consistent with our interpretation that

D2-Mut exhibits modestly more constitutive activity and substantially greater sensitivity to dopamine than D2-WT. Overall, D2-Mut is a G protein-biased receptor with enhanced constitutive activity. (VA Merit Review)

M27. A Semi Mechanistic Pharmacokinetic Model to Understand the Metabolic Conversion of Mitragynine to 7-Hydroxymitragynine

Abhisheak Sharma, Tamara King, Shyam Kamble, Francisco León, Julius Hertin, Till-Arved F. Ehrenhart, Christopher McCurdy, Bonnie Avery*

Mitragynine, the major alkaloid of kratom (Mitragyna speciosa), is believed to be predominantly responsible for kratom's psychoactive effects. It has been shown that mitragynine is metabolized to 7-hydroxymitragynine, which is also a minor alkaloid of kratom, that is 13- and 46-fold more potent than morphine and mitragynine, respectively. The potent kratom alkaloid, 7-hydroxymitragynine, also produces tolerance, cross-tolerance to morphine, and physical dependence. Thus, it is necessary to understand the rate and extent of metabolic conversion of mitragynine to 7-hydroxymitragynine. Oral (20 mg/kg) and intravenous (2.5 mg/kg) pharmacokinetic studies of mitragynine were performed in female Sprague Dawley rats (N=6, each), and concentrations of both mitragynine and 7-hydroxymitragynine were determined in plasma and brain samples using a validated ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method. Concentrations of mitragynine and 7-hydroxymitragynine in brain 24 h post-dose were 325.6 ± 99.1 and 15. 6 ± 5.7 ng/g for orally and 62.9 ± 31.5 and 0.9 ± 0.1 ng/g for intravenously dosed rats. The percentage area under curve (%AUC) of 7-hydroxymitragynine to mitragynine followed by oral and intravenous administration of mitragynine was found to be 9.1 ± 0.3 and 3.3 ± 0.3%, respectively. A comparatively higher metabolic conversion of mitragynine to 7-hydroxymitragynine following oral administration than intravenous route can be attributed to the intestinal metabolism of mitragynine. Based on the diagnostic plots, lowest Akaike's information criterion (AIC) and Schwarz criterion (SBC), a three-compartmental open model was found to be the best fit for both oral and intravenous concentration-time data of mitragynine (Phoenix NLME, version 6.3; Certara Inc, Missouri, USA). The pharmacokinetic model of mitragynine was further extended to describe its metabolic conversion to 7-hydroxymitragynine (Figure 1). After successful fitting, both mitragynine and 7-hydroxymitragynine concentration-time data, conversion coefficient of the parent to the metabolite was found to be 0.04 ± 0.002 h-1. The developed pharmacokinetic model can be further extended to predict human exposure of 7-hydroxymitragynine using basic allometric principles.

M28. Can Axons Finding Their Way in Prefrontal Cortex in Neurodevelopmental Disorders?

John Huguenard, Tanya Weerakkody, Brielle Ferguson, Christopher Makinson*

Autism Spectrum Disorder (ASD) is a complex heterogeneous neurodevelopmental syndrome with genetic and environmental risk factors. Infection during pregnancy is strongly implicated as an environmental factor, with maternal immune activation (MIA) identified in the causative pathway. However, a mechanistic understanding of MIA induced alterations in brain function and accompanying social behavior remains elusive. Here, using a mouse MIA model, we find in offspring a profound and persistent impairment in the excitability of medial prefrontal cortex (mPFC) – a key locus of social cognition and ASD pathology. Specifically, we find a novel structural disorganization of the axon initial segment and blunted spike transmission along the axon. Transcriptomic analysis identified L1cam deficiency as a likely key mediator of the structural and functional impairments. Inactivation of L1cam in mPFC reproduces impairment in social behavior. These results demonstrate a fundamental alteration in the output of mPFC neurons in ASD. Large-scale synaptic deficits in excitation and inhibition within the mPFC were primarily attributed to reduced presynaptic activation of layer 5 pyramidal neurons, which corresponded to defective action potential initiation in whole-cell patch clamp recordings. In addition, orthodromic axonal spikes, as detected by axon-attached recordings, were significantly attenuated in MIA offspring and exhibited reduced propagation velocities. Finally, axon initial structure, based on staining for Ankyrin-G was disrupted, show an anatomical basis for altered axon function. Based on these results, we identify presynaptic axonal excitability as a novel contributor to ASD-related mPFC dysfunction.

M29. Rare Genetic Variants in Monoamine Transports as a Risk Factor for Neuropsychiatric Disease? Insights From a Population Based Case-Control Sample

Freja Herborg, Vivek Appadurai, Alfonso Demur, Thomas Werge, Ulrik Gether*

The monoaminergic circuits of the brain have long been implicated in most of the common neuropsychiatric diseases. Still, it is not clear if disease-relevant circuit dysfunctions can originate in monoaminergic neurons and sensitise individuals to develop neuropsychiatric disease. The monoamine transporters (MAT) are selectively expressed in monoaminergic neurons and serve as key regulators of monoaminergic neurotransmission and as principal targets for neuropsychiatric therapeutics. Using exome sequencing data from 5554 controls and 14283 cases diagnosed with attention deficit hyperactivity disorder, (ADHD, N=5040), autism spectrum disorder (ASD, N=5694), schizophrenia (N=3686), depression (N=2967), or bipolar disorder (N=1528),

we address if disruptive genetic variants in the MAT genes (SLC6A2/NET, SLC6A3/DAT, SLC6A4/SERT, and SLC18A2/VMAT2) associate with neuropsychiatric disease. We found a significant excess of both 'loss of function' (LoF) variant sites (P=0.013) and number of carriers (P=0.046), in patients diagnosed with mental disorders. Moreover, analysis of disease associations at single gene level, uncovered a complete absence of LoF variants in NET/SLC6A2 in control individuals with resulting significant disease associations between NET/SLCA2 and ASD, schizophrenia, depression and bipolar disorder. A nominal significant disease association was also found for DAT/SLC6A3 and ADHD. These findings provide new support to the monoamine hypothesis of neuropsychiatric disease by directly linking inherited changes to MAT function to an increased the risk of neuropsychiatric disease.

M30. Cocaine Actions on Cortico-Striatal Circuitry: A Focus on Cholinergic Interneurons

Michael Authement, J.H. Shin, Veronica Alvarez*

Cholinergic interneurons (CINs) of the striatum are thought to play a critical role in behavioral flexibility and dysfunction of CINs may underlie the pathology of compulsive behaviors that are expressed in drug abuse. Although CINs account for only 1% of striatal neurons, they are the major source of acetylcholine in the striatum. Furthermore, recent studies have identified another critical function of CINs: triggering dopamine release. Direct and indirect activation of CINs through cortical and thalamic inputs can evoke dopamine release independent of midbrain dopaminergic neuron firing. Therefore, we hypothesize that if drugs of abuse have effects on CIN physiology, they would not only affect the levels of acetylcholine in the striatum, but also affect this novel form of striatal dopamine signaling. The central goal of this study is to identify the mechanisms underlying the acute and chronic effects of cocaine, a stimulant drug of abuse, on CIN activity and on synaptic inputs to CINs. Specifically, we are focusing on glutamatergic inputs from the prefrontal cortex (PFC) onto CINs based on the well-known role of the PFC in behavioral flexibility and inhibitory control. Recordings from CINs in ex vivo brain slices showed that cocaine potently and dose-dependently depressed excitatory transmission from PFC inputs onto CINs. The mechanism underlying this acute depression appeared to be presynaptic and was not blocked with the D2 dopamine receptor antagonist sulpiride. Cocaine increased the spontaneous action potential firing in CINs by two-fold, and this effect was blocked with a serotonin receptor antagonist, ketanserin, or D1/D5 dopamine receptor antagonist, SCH-23390. After repeated administration of cocaine over a 5-day period, the excitability of CINs was decreased and remained lower for up to 21 days after the last cocaine administration. Thus, while cocaine acutely increases CIN firing, chronic exposure to cocaine produces a long-lasting depression

of firing, a plasticity in the opposite direction. These studies are revealing novel actions of cocaine on cortico-striatal circuitry that we speculate may contribute to the loss of inhibitory control and the behavioral inflexibility that characterizes compulsive cocaine use.

M31. Exploration of Posttranscriptional and Translational Regulation in Depolarized Neuroblasts

*Dylan Kiltschewskij, Murray Cairns**

Experience-dependent modification of synaptic structure and function are driven by complex temporospatial patterns of mRNA translation. Although the translational profiles of a subset of excitation-dependent mRNAs have been determined, the global dynamics of translation and the functional contribution of posttranscriptional regulatory factors, such as small non-coding RNA, remain poorly understood. In the current study, we explored excitation-sensitive patterns of translational activity by conducting ribosome profiling on differentiated SH-SY5Y cells at several time points after repeated K+ depolarization. This was carried out in conjunction with mRNA sequencing to investigate whether modulation of mRNA translation matched underlying profiles of mRNA abundance, while small RNA sequencing was additionally used to determine the functional role of miRNA in this system. Differential expression analysis revealed translational fluctuations were most pronounced immediately after depolarization, wherein gene products involved in synaptic function were transiently prioritized. Surprisingly, this translational activity exhibited poor concordance with changes in mRNA abundance, however these factors progressively became synchronized during the experimental time-course. Although the most prominent change in miRNA expression coincided with this early excitatory phase, expression of these molecules was found to be more inversely proportional to mRNA stability than translation, with the number of expressed miRNA binding sites determining the magnitude of mRNA destabilization. Our findings indicate neuronal excitation generates complex profiles of mRNA translation, which are initially regulated independently of underlying changes in mRNA abundance or miRNA expression. We suspect alternative regulatory systems play a role in coordinating early patterns of excitation-associated translational activity in neuronal cells.

M32. NRAP-1 is a Protein Ligand for the NMDAR Amino-Terminal Domain

Dayton Goodell, Jerry Mellem, Ning Lei, David Madsen, Andres Maricq*

The NMDA-receptor (NMDAR) subtype of ionotropic glutamate receptors (iGluRs) has fundamental roles in the processing and encoding of information, and in humans, defects in NMDAR signaling are a hallmark of many

neurological disorders. Recently, a genetic screen for modifiers of NMDAR function in C. elegans identified a presynapticaly secreted protein, NRAP-1, that is required for the gating of NMDARs. Additionally, NRAP-1 is rate limiting for NMDAR function, and thus is likely to control the magnitude of NMDAR signaling. Here we show that NRAP-1 is a NMDAR amino-terminal ligand with nM affinity sufficient to partially gate open the NMDAR in the absence of glutamate. Furthermore, we identify the domains of NRAP-1 that modify NMDAR gating. We also demonstrate that select vertebrate proteins that contain NRAP-1 domains when modified with simple amino acid substitution also gate C. elegans NMDARs. Because of the deep evolutionary conservation of iGluRs and glutamatergic signaling, we anticipate that similar signaling mechanisms might also contribute to the regulation of vertebrate NMDAR signaling. Additionally, comparisons of the evolutionary divergence of NMDAR gating made possible by the results of this study provide fundamental insights into the design and function of NMDARs allowing for new conceptual framework for drug discovery that could ultimately motivate novel approaches for therapeutic intervention in neurological disease characterized by disrupted NMDAR function.

TUESDAY, JANUARY 28, 2020 • 3:30 P.M. - 4:30 P.M. • JEFFERSON/MADISON

T1. Hierarchical Cue Control of Cocaine Seeking in the Face of Cost

Anne Collins, Benjamin Saunders*

Drug addiction is characterized by intermittent, persistent drug seeking despite rising costs. Drug-associated cues are a powerful trigger of this behavior, capable of inciting relapse in recovering addicts. We set out to model three key aspects of human drug use in rats: the intermittent, binge-and-stop nature of drug intake, the motivational conflict of drug seeking in the face of escalating negative costs, and the ability of different types of drug cues to modulate seeking and spur relapse. Critically, we found that the ability of proximal cues to trigger relapse was gated by the presence of a global cue signaling drug-availability within the animal's environment, suggesting that hierarchical cue interactions exert an important modulating influence on drug-seeking motivation. Dopamine release within the nucleus accumbens core (NAc) has been implicated in cue-induced relapse of drug seeking. It is less clear, however, if dopamine signaling may encode hierarchical drug-related learning states where drug cues interact to guide seeking. To address this, we measured changes in dopamine receptor activity within the NAc core with fiber photometry, using the genetically encoded dopamine sensor dLight. Our preliminary data suggests that the dopaminergic signaling profile in the NAc core changed throughout binge-like drug use, as rats learned to pattern their intake in response to global

signals of drug availability. Together these results demonstrate hierarchical cue control of drug seeking despite cost, and point to a role for NAc core dopamine in this process.

T2. In Vivo Identification and Modulation of Appetitive Memory-Related Circuit Elements in the Mouse Prefrontal Cortex

Roger Grant, Elizabeth Doncheck, Elizaveta Romanova, James Otis*

The prefrontal cortex (PFC) is a hotbed of heterogeneous cell types that integrate sensory, motivational, and memory-related information to help guide learned behaviors. However, activity in PFC can become maladaptive in individuals suffering from substance use disorder (SUD), with that activity being a reliable predictor of future relapse. Despite the known involvement of PFC, in particular the prelimbic sub-region of medial PFC (PL-mPFC), how heterogeneously-responding cortical cell types contribute to reward-seeking behaviors is not yet fully understood. Here, we use in vivo two-photon calcium imaging to define multiple excitatory PL-mPFC cell clusters that respond in unique manners to reward-related cues. In addition, we find that inhibition of noradrenergic receptors, primary neuromodulator receptors that influence cue-induced reward seeking, with the pharmacological antagonist propranolol (i.p., 10 mg/kg) can persistently impair cue-driven sucrose seeking in a Pavlovian conditioning task. Furthermore, we find that cue encoding in excitatory cell clusters of the PL-mPFC was also perturbed under these conditions. Our research suggests that noradrenergic signaling is a primary mechanism that allows cues to drive reward-seeking behavior under normal conditions, likely by modifying the cue-encoding properties of excitatory output neurons in PL-mPFC. Next, we aim to understand how noradrenaline influences cue encoding and reward-seeking behaviors in a rodent model of drug addiction.

T3. Investigating the Effects of Controllable Stress on Future Behavioral and Neuronal Responses to Reward- and Drug-Associated Cues

Kayla Siletti, Kyle Brown, Michael Saddoris*

Even after prolonged periods of abstinence, stress can potently trigger drug cravings and induce relapse. Uncontrollable stress prior to exposure to drug-associated cues (e.g. paraphernalia) can generate enhanced vulnerability to relapse. However, perceived control over a stressor produces vastly different behavioral outcomes. These stressors, while still aversive, have been shown to endow animals with resilience against future stressors, even when these stressors occur in different contexts or require unique actions. In an animal model of stressor controllability, rats can turn a wheel to escape tail-shock

(escapable stress; ES). Yoked animals receive physically identical shock but cannot turn a wheel; thus, they have no such perception of control (inescapable stress; IS). After a single session of repeated trials, ES-experienced animals express reduced neophobia and hypervigilance, characteristic of stress-naïve home-cage controls, whereas their IS counterparts exhibit heightened states of anxiety.

Animals with a history of chronic cocaine self-administration similarly demonstrate different behavioral outcomes following controllable and uncontrollable stressors. These stressors differentially modulate how cocaine-experienced animals learn about and respond to cues associated with natural and drug rewards. Here, we demonstrate that electrophysiological responses in the nucleus accumbens to reward-predictive cues during abstinence are dampened following exposure to uncontrollable stress, but controllable stress protects against such deficits in cue responsivity. Ongoing work is examining how these unique stress experiences may alter drug-associated cue responses, in ways that accelerate the extinction of drug-seeking behaviors and mitigate neuronal adaptations taking place over the first 30 days of drug abstinence. Collectively, these data suggest that control over stressful experiences or lack thereof may produce opposing effects on reward- and drug-seeking.

T4. Kappa-Opioid Receptor Antagonism Reverses Heroin Withdrawal-Induced Allodynia

Renata Marchette*, Adriana Gregory-Flores, Brendan Tunstall, Agnieszka Sulima, Kenner Rice, Leandro Vendruscolo, George Koob

Although opioids are potent analgesics, chronic opioid use leads to allodynia (defined as pain due to a stimulus that is not normally painful) that is observed during withdrawal and contribute to opioid addiction. There is evidence supporting the involvement of kappa opioid receptors (KOR) in allodynia in chronic pain models. However, the role of KOR in opioid withdrawal-induced allodynia/hyperalgesia remains to be determined. Because KORs are upregulated in brain regions in opioid dependent rats, we hypothesize that KOR antagonist would revert opioid withdrawal-induced allodynia. To test our hypothesis, we first investigated the selectivity of 5'-guanidinonaltrindole (GNTI) in antagonizing the analgesic effect of KOR agonism in the tail flick test. We found that GNTI blocked the analgesia induced by U50,488, a selective KOR agonist. To investigate the potential of GNTI to reverse opioid withdrawal-induced allodynia, male and female Wistar rats received daily injections of heroin (diamorphine hydrochloride, 2-6 mg/kg, s.c.) and were tested for mechanical sensitivity with an electronic von Frey (eVF) 4-6 h into heroin withdrawal. Both male and female, heroin-treated rats exhibited reduced paw withdrawal thresholds compared with the saline group, indicating the development of allodynia. Females required higher doses of heroin. Next, the

rats received vehicle (saline, 1 mL/kg), 24 h before eVF testing and on the next day, GNTI (30 mg/kg, s.c.), testing was repeated 24 h, 96 h, 7 and 14 days after GNTI treatment. In male and female rats, paw withdrawal thresholds were significantly higher after GNTI treatment, reversing heroin withdrawal-induced allodynia in rats of both sexes, an effect that lasted for at least 96 h. These findings indicate, a functional role of KOR in the allodynia induced by heroin withdrawal in both sexes.

T5. Intratelencephalic and Pyramidal Tract Neurons Differentially Mediate Cocaine Sensitization and Conditioned Taste Aversion

Elizabeth Crummy, Aaron Garcia, Isah Webb, Reiley Durre, Susan Ferguson*

Intratelencephalic (IT) and Pyramidal Tract (PT) are two classes of glutamatergic cortical projection neurons that exhibit unique morphology, firing patterns, and connectivity. However, little is known about their functional role in mediating behavioral outputs. We have recently found distinct roles of IT and PT neurons in anterior cingulate cortex (ACC) in the appetitive and aversive components of cocaine use Specifically, inactivation of IT neurons blunted a cocaine-induced sucrose aversion, whereas PT inactivation increased the cocaine place preference and transiently altered cocaine sensitization. Nonetheless, how IT neurons influence additional dimensions of substance use, including the locomotor sensitization to cocaine, has yet to be elucidated. To address how IT neurons contribute to sensitization and if IT inactivation inherently alters aversive processing, IT neurons were chemogenetically modulated in ACC. Rats were either pretreated with CNO (5 mg/kg, i.p.) or vehicle (5% Dimethyl sulfoxide in sterile water, i.p.) 30 minutes prior to treatment with either cocaine (15 mg/kg, i.p.) or saline (0.9%, i.p.) for seven sessions. Two weeks following the last session, all groups were given a challenge in cocaine injection (10 mg/kg). To assess the inherent effects of IT inactivation on aversive responses, rats were given access to a 15% sucrose solution followed by i.p. injections of CNO or vehicle and subcutaneous injections of saline. Inactivation of IT neurons in ACC heightened locomotor activity during early cocaine exposure, in contrast to PT inactivation. Furthermore, IT inhibition is not in of itself aversive, suggesting that alterations of a cocaine-induced CTA was not just due to loss of IT activity. Ongoing work will confirm these findings. Additionally, examining the role of these cell types in contingent cocaine administration and relapse behaviors will provide greater understanding of their role in processing motivational facets of substance use.

T6. Neurobiological Correlates of Low Nicotine and Cannabis Exposure

*Hugh Garavan**

The increased availability of cannabis (legalization and decriminalization) and nicotine (vaping) has raised concerns that use of these substances will increase in adolescence, a period during which the developing brain may be especially susceptible to the effects of substances with abuse potential. Longitudinal studies of adolescents can help identify potential consequences of substance exposure. In this poster, I will present data from the IMAGEN study, a ten-year longitudinal study of 2,000 European adolescents. This study contains extensive phenotyping, including functional and structural brain imaging, and genotyping with assessments at ages 14, 16, 19 and 23. The analyses of the brain data at age 14 show structural differences associated with very light use (1/2 cigarettes; 1/2 joints). Analysis of the longitudinal data suggest that these effects did not precede use. Furthermore, a magnified effect (volume reduction in the vmPFC) in smokers with a high-risk alpha5 nicotinic receptor gene suggests the smoking effects are mediated, in part, by the nicotinic system. The widespread subcortical effects associated with light cannabis use are in regions high in CB1 receptors, adding evidence that this effect may be related to the cannabinoid system. The implications of these observations for theories of addiction will be discussed.

T7. Excitation of Nucleus Accumbens D1 Medium Spiny Neurons and Facilitation of Dopamine Release via Activation of the Muscarinic M1 Receptor Regulates Motivated Behavior

Samantha Yohn*, James Maksymetz, Weilun Qian, Ellen Rieth, Zixiu Xiang, Joseph Cheer, Erin Calipari, Craig Lindsley, Jeff Conn

Motivational symptoms are debilitating features of several neuropsychiatric disorders and are highly correlated to long-term treatment outcomes. Recent studies have highlighted the regulatory role of nucleus accumbens (NAc) dopamine (DA) release and D1 medium spiny neurons (MSNs) in motivated behavior. Reductions in NAc DA release and augmented excitability of D1-MSNs have been correlated with anhedonic-like phenotypes, suggesting that agents that modulate DA release and D1-MSN activity may be efficacious for motivational dysfunctions. Gq/11-coupled muscarinic acetylcholine (mACh) M1 receptors are highly expressed in the NAc and have been reported to regulate the transition states of striatal MSNs and DA transmission. Herein, we investigate the ability of highly selective M1 compounds to modulate NAc microcircuitry. We assessed M1 activation on NAc DA release via in vivo fast scan cyclic voltammetry, examined real-time activity of M1 activation on NAc

D1-MSNs in vivo by recording calcium (Ca2+) transients in D1-cre mice, and evaluated motivated behavior through use of an effort-related choice assay. Excitingly, we found that activation of M1 increased NAc DA release by 50% compared to baseline conditions and enhanced D1-MSNs Ca2+ transient frequency and amplitude compared to saline-control conditions. Moreover, pharmacological activation of M1 increased selection of higher effort alternatives. Together, these experiments may help to elucidate precise neural circuit dynamics that underlie aberrations in motivated behavior, which could lead to the development of safe and effective treatments for motivational dysfunctions.

T8. DG3-80: A Novel Fluorescent DAT Ligand Ideal for Live Super-Resolution Microscopy

Amy Newman, Daryl Guthrie, Carmen Herenbrink, Matthew Lycas, Therese Ku, Alessandro Bonifazi, Luke Lavis, Ulrik Gether*

The dopamine transporter (DAT) plays a critical role in regulating dopamine homeostasis and is the principle target for widely abused psychostimulants, such as cocaine and methamphetamine. Alteration in dopamine signaling and DAT function is also associated with neurological and psychiatric disorders including Attention Deficit Hyperactivity Disorder and Parkinson's Disease. Nonetheless, little is known about the cellular distribution and trafficking of endogenously expressed DAT in these conditions and how they are affected by drugs of abuse or prescription medications. One approach to begin to understand mechanisms underlying the molecular and cellular processes governing the activity and availability of DAT in the presynaptic nerve terminals is to use fluorescent tools. We have developed high affinity and DAT-selective fluorescent small molecules that permit the detection and tracking of DAT, which in turn, allows us to study the plasma membrane surface dynamics and distribution of DAT in dopaminergic neurons. Previously, JHC1-064, which like cocaine binds to an outward facing conformation of DAT, has been used to visualize DAT trafficking. We have recently optimized and validated a new fluorescent tool, DG3-80, that may be superior for super-resolution microscopy. This novel DAT ligand links the Janelia Fluor 549 dye to a cocaine-derived tropane scaffold via a polyethyleneglycol linker and allows the detection of endogenously expressed DAT in CAD cells and DA neurons using dSTORM.

T9. Behavioral, Autonomic, and Neural Evidence of Sex Differences in the Human Reward System

Katherine Warthen, Alita Boyse-Peacor, Keith Jones, Benjamin Sanford, Tiffany Love, Brian Mickey*

Affective disorders and addictions, along with other psychiatric disorders, affect men and women differently. Given the extent that the reward system is involved in these disorders, we hypothesized that reward behavior and physiology would differ between the sexes. We quantified the sex differences in reward responses in 221 healthy young adults during a monetary incentive task that engages the mesoaccumbal pathway and salience network. Stimuli varied by salience and valence (behavioral relevance vs. positivity and negativity). We measured reward related traits, task behavior, autonomic activity as reported by skin conductance, and fMRI neural responses to generate evidence spanning multiple neurobehavioral levels. Men reported higher levels of reward sensitivity, fun seeking, and appetitive motivation relative to women. Men also showed greater subjective arousal ratings, behavioral accuracy, and skin conductance responses. In imaged subjects (n=44), men showed greater responses to salience in the nucleus accumbens, midbrain, anterior insula, and dorsal anterior cingulate cortex. Responses to valence as measured by behavioral autonomic, and neural sensitivity did not differ between the sexes, indicating that these differences were present in both win and loss conditions. We reveal novel and robust sex differences in the processing of salient stimuli. These outcomes indicate a neurobehavioral basis for sexual dimorphism in disorders of the reward system.

T10. Excitatory Regulation From the Parabrachial Nucleus to the Ventral Tegmental Area Mediates Unanticipated Long-Term Memory of Aversion

Smriti Mongia, Huiling Wang, Shiliang Zhang, Carlos Mejias-Aponte, Jorge Miranda-Barrientos, Marisela Morales*

The ventral tegmental area (VTA) is a brain structure well known for containing dopamine neurons that have been implicated in motivation, addiction, decision making, aversion and pain. While it has been suggested that different types of VTA dopamine neurons participate in these different behaviors, emerging findings suggest that some of these behaviors may also be mediated by VTA non-dopamine neurons. In this regard, we have recently demonstrated that the VTA has a subset of glutamatergic neurons (expressing vesicular glutamate transporter 2, VGluT2 mRNA) that are involved in aversion. Here, we conducted monosynaptic rabies tracing studies to determine the upstream neurons that may regulate the activity of VTA glutamatergic neurons. From these tracing studies, we found that the VTA glutamatergic neurons received

inputs from the parabrachial nucleus (PBN), a brain area implicated in aversive behavior. Next, we determined the phenotype of PBN neurons innervating the VTA by using a combination of chemical neuronal tracing and in situ hybridization and found that the vast majority of PBN neurons that innervate the VTA expressed VGluT2 mRNA. Given that these findings suggest that PBN-glutamatergic neurons excite VTA-glutamatergic neurons, we combined viral tracing techniques with immuno ultrastructural analysis, and found that axon terminals from PBN neurons (containing VGluT2-protein) established asymmetric (excitatory type) synapses on VTA VGluT2-positive neurons. To confirm the excitatory nature of the PBN synapses on VTA-glutamatergic neurons, we used a combination of viral tract tracing, optogenetics and slice electrophysiology and found that glutamate released from PBN-glutamatergic innervations evoked the firing of VTA-glutamatergic neurons. Next, by combination of optogenetics and behavior analysis, we found that VTA laser-induced release of glutamate from PBN inputs resulted in place aversion. Moreover, in the absence of laser-stimulation, this aversion was maintained for up to 60 days. In summary, we provide compelling evidence indicating that glutamatergic inputs from the PBN to the VTA are part of a neuronal network that mediates long-lasting memory of aversive signaling.

T11. Genetic Dissection Reveals Different Roles for Intrinsic and Extrinsic Catecholaminergic Innervation of the Cognitive Cerebellum

Erik Carlson*, Avery Hunker, Stefan Sandberg, Shelby Johanson, Timothy Locke, Paul Phillips, Larry Zweifel

We have previously shown that the dopamine D1 receptor marks a population of neurons in the LCN regulates cognitive performance on several tasks related to attention and working memory and has connections with other parts of the brain that are classically involved in these functions. We hypothesized that the locus ceruleus (LC) is the source of norepinephrine release in LCN, that Purkinje cells (PCs) expressing tyrosine hydroxylase (Th) are the source of dopamine release in LCN. We have mapped LC projections to LCN, and analysis revealed distinct projections from the locus ceruleus, but no other nuclei outside of the cerebellum known to produce catecholamines. When we injected DBH-IRES-Cre; TdTomato mice with green retrobeads in LCN, we found overlap of the retrobeads and tomato staining, suggestive of LC projections to LCN. LC stimulation results in catecholamine release in the LCN is observed with cyclic voltammetry. We also mapped the expression of Th in a subset of PCs in the cerebellum. Deletion of Th in LCN results in abnormal performance on working memory, response inhibition, and sensory discrimination behaviors. Th lox/lox mice were injected with CAV-Cre (retrograde virus) into LCN and trained on either an impulsivity or a delayed

alternation task. Littermate controls were injected with CAV2 encoding the fluorophore, zsGreen. Tyrosine hydroxylase was reduced by 75% in the LCN verified by Western blot. LCN TH knockout mice showed more impulsive pressing than littermate controls. LCN TH knockout mice showed impairment in learning delayed alternation. Furthermore, we used two approaches to target Th expression in either PCs or the LC->LCN projection. First, we selectively knocked out Th in PCs by crossing a Pcp2-Cre line with Th lox/lox mice, in which the LCN Th expression is reduced by 50%. Second, we used a combinatorial viral approach to specifically knock out Th expression in the LC->LCN projection by injecting Cav-Cre in the LCN and a CRISPR Th knockout construct (AAV1-FLEX-SaCas9-U6-sgTh) into the LC. We then examined a selection of behaviors and found differing effects in Pcp2-Cre;Th lox/lox mice and mice injected with both LC: AAV1-FLEX-SaCas9-U6-sgTh and LCN: Cav-Cre, suggesting different roles for each of these sources of catecholamines in the LCN.

T12. VTA Glutamate Neurons Promote Aversion by Activation of mPFC Parvalbumin Neurons

Huiling Wang, Huikun Wang, Flavia Barbano, Marisela Morales*

Dopamine inputs from the ventral tegmental area (VTA) to the medial prefrontal cortex (mPFC) have been implicated in neuropsychiatric pathologies for decades. Recent findings indicate that the mPFC is also innervated by VTA neurons expressing the vesicular glutamate type 2 (VGluT2). However, it is unclear the extent to which the subdivisions of the mPFC are targeted by the different subclasses of VTA VGluT2 neurons. In this study, we injected the retrograde track tracer fluorogold (FG) in either the prelimbic (PrL) or infralimbic (IL) cortex of wild type rats, and phenotyped the VTA FG-positive (mesocortical) neurons by a combination of in situ hybridization (to detect VGluT2 mRNA or glutamate acid decarboxylase, GAD mRNA) and immunohistochemistry (to detect both FG and tyrosine hydroxylase [TH]). For the mouse analysis of mesocortical VGluT2 neurons, we injected the AAV-DIO-eYFP viral vector into the VTA of VGluT2::Cre transgenic mice. In these mice, we also injected FG into the PrL or IL cortex, and evaluated VTA co-expression of FG and eYFP neurons. In rats and mice, we found that (1) both IL and PrL cortex received inputs from VTA neurons, but these VTA neurons provided 4.4 times more inputs to the IL than PrL cortex. (2) Four classes of VTA neurons innervated the mPFC: TH-only, VGluT2-only, dual VGluT2-TH, and GABA-only. (3) The VTA inputs to mPFC were mostly from VGluT2-only, TH-only and dual VGlu2-TH neurons, and less frequently from dual VGluT2-GABA or GABA-only neurons. By photoactivation of mPFC VGluT2 inputs from VTA neurons, we found that this mesocortical VGluT2 pathway induced conditioned place aversion, which depended on activation of both glutamate and GABA receptors. Next, we determined the type of IL

neurons activated by the mesocortical VGluT2 pathway and found that this pathway induced c-Fos expression in parvalbumin (PV) GABA interneurons. By electrophysiological and ultrastructural analysis, we found that PV neurons of the IL cortex were the major target of VTA VGluT2 terminals (Dr. Zhang's abstract). Our findings indicate that the VTA provides a glutamatergic excitatory input to a subpopulation of IL cortical PV-GABAergic neurons, and that activation of these PV neurons inhibits neighboring pyramidal neurons, promoting aversive behavior.

T13. Characterization of the Affective State and Neural Correlates During Empathic Behavior in Rats

Stewart Cox, Brogan Brown, Angela Kearns, Carmela Reichel*

Prosocial behaviors, such as social interaction and empathy, are imperative for an adaptive social structure by the allowance for personal understanding of the perceived valence of others. Further, these behaviors may play a role in the underlying pathology of numerous cognitive disorders. Research suggests animals will behave prosocially in the hopes of receiving social reward, but only recently has it been intimated some animals are capable of behaving empathically. Empathy is defined as the capacity for one to experience the valence of another, thereby generating a response more appropriate to another's emotional situation than one's own, independent of personal gain. We have developed a model of empathic behavior that requires the animal to pull a chain to release a distressed conspecific from 100mm of water via an automated guillotine door. Importantly, we designed the apparatus to eliminate the social reward as a motivator for the observed behavior. We have characterized this model to ensure specificity of the release behavior through a series of experiments varying the level of distress to the conspecific. Here we extend our previous work to female rats. We initially hypothesized that female rats would show greater empathic processes relative to males, but both learn to release a conspecific at the same rate. During the task we collected ultrasonic vocalizations (USVs) to begin to identify the rats' affective state and data are being analyzed with the detection software DeepSqueak. To date, we have identified several different categories of USV calls based on call Hz with the range of prosocial and distress calls. Future, experiments will evaluate the role of several neural substrates, including the insular cortex and basolateral amygdala, during the task. Our lab's model allows for an evaluation of empathic behavior in rats, as well as an elucidation of the neural underpinnings of empathy and how they are affected by cognitive disorders like SUD.

T14. The Dynamics of Brain Connectivity at Rest Underpins Performance in Task

Yvonne Yau, Filip Morys, Alain Dagher*

Flexible human cognition depends on the ability of brain circuitry to transiently express various functional configurations, coined intrinsic connectivity networks (ICNs). Time-varying functional connectivity (tvFC) quantitatively characterizes reoccurring brain patterns (i.e., "states") and their dynamic functional properties. These metrics allow us to observe the dynamic interplay within and between ICNs at the time scale that cognitive processes operate at. Here, we employed a data-driven approach to assess tvFC based on established techniques including: whole-brain independent component analysis to identify ICNs and k-mean clustering of fixed-length sliding windowed correlation matrices to identify brain states. 4 connectivity states were identified from our resting state fMRI data and were tested against behavioral performance in a perceptual decision-making task undertaken in the scanner beforehand (N=55). Participant's accuracy in task were related to a greater number of transitions between states (r=.346, p=.013) and to dwell time in an anticorrelated state (r=.495, p=<.001) which exhibited high modularity within the default mode network and negative connectivity to motor-visual systems. Moreover, the more similar the brain connectivity pattern in task was to the anticorrelated state at rest, the better their accuracy performance (r=.4077, p=.003). In a post-hoc analysis, we found participants with longer dwell time in the anticorrelated state at rest demonstrated greater caudate signal in task during the deliberation phase. Caudate activity may represent a dopaminergic stopping signal to slow the deliberation process and promote greater accuracy. Taken together, these findings suggest that better task performance may be associated with higher flexibility in network reconfiguration and the propensity to stay in more optimal brain configurations both at rest and in task. Time-varying approaches to network neuroscience could reveal insights into the neural configurations that underpin individual differences in human cognition.

T15. The Effect of Subthalamic Nucleus Deep Brain Stimulation on Effort Discounting

Guillaume Pagnier, Wael Asaad, Michael Frank*

Parkinson's disease (PD) is a common neurodegenerative disease affecting 1% of the elderly population. High frequency deep brain stimulation (DBS) in the subthalamic nucleus (STN) improves motor symptoms, but its precise mechanism of action is still unclear. In cognitive tasks, DBS can lower the 'decision threshold' and increase impulsivity by disrupting the STN theta-band modulation in response to cognitive conflict. These results contrast with the effects of dopaminergic medication (which alter the weighting of benefits vs

costs of decisions), and have been interpreted in terms of an informational lesion induced by DBS. Here we evaluate whether low vs high frequency stimulation in different STN contact locations (dorsal vs ventral) can have differential effects on decision threshold or cost-benefit decision making in a physical effort-discounting task. We present behavioral data and spontaneous eye blink rate data to clarify STN DBS' effects on cost/benefit decision making.

T16. Mechanisms of Prefrontal Circuit Assembly

Cassandra Klune, Benita Jin*, Christopher Gabriel, Rakasa Pattanaik, Vincent Xu, Laura DeNardo

Critical functions including memory guided behaviors, decision making, and social behaviors are all dependent on the medial prefrontal cortex (mPFC). mPFC is interconnected with a distinctly large set of brain regions, each with unique behavioral functions. Neurons in mPFC undergo a protracted period of development which likely explains why its circuitry is implicated in numerous neuropsychiatric disorders. Despite the crucial function and unique vulnerability of mPFC circuitry, the mechanisms underlying the assembly of these circuits are not known. Using viral approaches to label mPFC projection neurons in the postnatal brain, we are mapping the developmental time course of mPFC synapse formation in select target regions including the nucleus accumbens and basolateral amygdala. In conjunction within situ hybridization to label transcripts for synaptic adhesion proteins, we are also identifying genes poised to specifically wire distinct aspects of mPFC circuitry. Using these genes as footholds, we will then manipulate mPFC circuit assembly to link key events in the maturation of specific mPFC connections to the emergence of adaptive behaviors over development. These experiments will provide insights into the molecular specificity within mPFC projection neurons that allow them to properly assemble, and how their assembly contributes to the maturation of complex behaviors.

T17. Diet Modulates Brain Network Stability, a Biomarker for Brain Aging, in Young Adults

Lilianne Mujica-Parodi*, Anar Amgalan, Syed Sultan, Botond Antal, Xiaofei Sun, Steven Skiena, Andrew Lithen, Eva Maria Ratai, Corey Weistuch, Sindhuja Govindarajan, Helmut Strey, Ken Dill, Steven Stufflebeam, Richard Veech, Kieran Clarke

Epidemiological studies suggest that insulin resistance accelerates progression of age-based cognitive impairment, which neuroimaging has linked to brain glucose hypometabolism. As cellular inputs, ketones produce 27% more ATP per unit oxygen than glucose. Here we test whether dietary changes are capable of modulating sustained functional communication between brain regions

(network stability), by changing their predominant dietary fuel from glucose to ketones, thereby increasing neuron-accessible ATP. We first established network stability as a biomarker for brain aging using two large-scale (N=292, ages 20-85 years; N=636; ages 18-88 years) 3T fMRI datasets. To determine whether diet can influence brain network stability, we additionally scanned 42 adults, ages <50 years, using ultra-high-field (7T) ultra-fast (800ms) fMRI optimized for single-participant-level detection sensitivity. One sample was scanned under standard diet, overnight fasting, and ketogenic diet conditions. To isolate the impact of fuel type, an independent overnight fasted sample was scanned before and after administration of a calorie-matched glucose and exogenous ketone ester (D-β-hydroxybutyrate) bolus. Across the lifespan, brain network destabilization correlated with decreased cerebral metabolic activity and cognitive acuity. Effects emerged at 47•4 years, with the most rapid degeneration occurring at 60•08 years. Networks were destabilized by glucose and stabilized by ketones, irrespective of whether ketosis was achieved with a ketogenic diet or exogenous ketone ester. Together, our results suggest that brain network destabilization may reflect early signs of hypometabolism, a biomarker for brain aging. Dietary interventions that result in ketone utilization increase neurometabolic efficiency, and thus may show potential in protecting the aging brain.

T18. VR Brain Exploration: Explore and Manipulate a 3D Brain to Alter CNS Mechanisms of Satiety and Hunger

*Bradley Tanner**

Neuroscience is quickly unraveling the neurochemistry and neurobiology behind obesity in increasingly fine detail. The model of the brain's impact on eating behavior is advancing rapidly. That model is expanding our understanding of mechanisms that regulate not only satiety and hunger but processes and structures that impact thermogenesis, basal metabolic rate, and activity. Unfortunately, the tools to explain this complicated system have not evolved as rapidly. We have been limited to charts, videos, and diagrams that are inadequate for most everyone except neuroscientists. With 3D models and the Oculus Quest, the capability of these tools now matches the complex world of the brain.

Learners in a variety of stages of life and disciplines can benefit from an exploration of the brain that allows direct exposure to and manipulation of key brain elements, neurotransmitters, receptors, and pathways. The potential value of a VR brain exploration can be realized by 1) researchers trying to explain their findings to other researchers, 2) clinicians trying to understand the mechanisms and impact of current and future drugs as well as chemicals such as cannabis, 3) patients attempting to understand why they are struggling with

the problem as well as the potential impact of interventions, and 4) the general public curious about a system that they deal with multiple times a day every day of their life, yet is mysterious.

A poster can discuss the power of the technology but to understand the potential of headset VR one must explore the VR brain in a truly immersive VR headset. The Oculus Quest is the first VR Headset with sufficient power and capability to deliver such an experience without wires or the need for a computer. The poster will thus include the opportunity to experience the potential of the technology to confer a 3D experience. In that experience, one is immersed in the complexity and beauty of a functional model of the brain emphasizing obesity-related structures and activity.

T19. Neuronal Protein Tyrosine Phosphatase 1B Drives the Progression of Amyloid β-Associated Alzheimer's Disease

Alex Stewart*, Konrad Ricke, Shelly Cruz, Zhaohong Qin, Kaveh Farrokhi, Michael Zasloff, Hsiao-Huei Chen

Alzheimer's disease (AD) is the most common neurodegenerative disorder, resulting in the progressive decline of cognitive function in patients. Familial forms of Alzheimer's Disease (AD) are tied to mutations in the amyloid precursor protein, but the cellular mechanisms that cause AD remain unclear. Neuroinflammation and amyloidosis from amyloid beta (Aβ) aggregates are implicated in neuron loss and cognitive decline. Since inflammation activates the protein-tyrosine phosphatase 1B (PTP1B), this could suppress many signaling pathways that activate glycogen synthase kinase 3β (GSK3β) implicated in neurodegeneration. Here, we show that either neuronal ablation or selective inhibition of PTP1B in a transgenic AD mouse model with Aβ pathology (hAPP-J20 mice) delays the decline of spatial memory and prevents hippocampal neuron loss, likely in part by restoring inhibition of GSK3β. Intriguingly, while systemic inhibition of PTP1B reduced neuroinflammation, neuronal PTP1B ablation did not, suggesting that inflammation is not sufficient to cause neuron loss and cognitive deficits without neuronal PTP1B. In addition, ablation of PTP1B reduced hippocampal Aβ plaque size, without altering Aβ protein concentration or plaque load. Our results demonstrate that neuronal PTP1B may drive AD-associated neurodegeneration and loss of memory. In addition, we present a new strategy to intervene in the progression of AD.

T20. Pomalidomide Analogues to Mitigate Neuroinflammation in Neurodegenerative Disorders – From Traumatic Brain Injury to Alzheimer's Disease

Nigel Greig, Daniela Lecca, Yoo Jin Jung, David Tweedie, Michael Scerba, Weiming Luo, Dong Seok Kim, Barry Hoffer, Chih-Tung Lin, Ling-Yu Yang, Jia-Yi Wang*

Traumatic brain injury (TBI) causes mortality and disability worldwide and, additionally, is a risk factor for chronic neurodegenerative conditions exemplified by Alzheimer's and Parkinson's disease. TBI can instigate acute cell death followed by secondary injury induced by microglial activation, inflammation, oxidative stress and autophagy in brain tissue, resulting in cognitive and behavioral deficits. We evaluated a new pomalidomide (Pom) analog, 3,6'-dithioPom (DP), and Pom as immunomodulatory agents to mitigate TBI-induced cell death, neuroinflammation, astrogliosis and behavioral impairments in rats challenged with controlled cortical impact TBI. Both agents significantly reduced the injury contusion volume and degenerating neuron number evaluated histochemically and by MRI at 24 hr and 7 days, with a therapeutic window of 5 hr post injury. TBI-induced upregulated markers of microglial activation, astrogliosis and the expression of proinflammatory cytokines, iNOS, COX-2, and autophagy-associated proteins were suppressed; leading to an amelioration of behavioral deficits with DP providing greater potency. Complementary animal and cellular studies demonstrated DP and Pom mediated reductions in markers of neuroinflammation and of both amyloid-beta- and alpha-synuclein-induced toxicity. DP is a novel and potent Immunomodulatory Drug (IMiD) that warrants further development as a new treatment option for acute and chronic neurodegenerative disorders characterized by a neuroinflammatory element.

T21. ITPKB, a Parkinson's Disease GWAS hit, Modulates A-Synuclein Pathophysiology in Cellular Models

*Daniel Apicco, Ed Guilmette, Evgeny Shlevkov, Justin Nicholatos, Catherine Nezich, G. Campbell Kaynor, Ellen Tsai, KD Nguyen, YuTing Liu, Andreas Weihofen, Jessica Hurt, Michelle Penny, Warren Hirst**

Inositol-1,4,5-triphosphate kinase B (ITPKB) is one of three protein kinases in the central nervous system that inactivates inositol-1,4,5-triphosphate (IP3), a second messenger that modulates intracellular calcium release from the endoplasmic reticulum (ER). Genome-wide association studies (GWAS) have identified common variants in the ITPKB locus that are associated with reduced Parkinson's disease (PD) risk (odds ratio = 0.92). Here, we investigate the effect of ITPKB modulation in cellular models of sporadic PD. Knockdown of endogenous ITPKB using shRNA, or treatment with the pan-ITPK inhibitor GNF362, increased intracellular calcium levels in mouse primary cortical neuron cultures, which led to the accumulation of calcium in mitochondria.

The increase in mitochondrial calcium following ITPKB inhibition was associated with enhanced mitochondrial respiration, increased ATP production, accumulation of reactive oxygen species, and activation of caspases. Further, the effect of ITPKB inhibition on mitochondrial respiration was prevented by pre-treatment with pharmacological inhibitors of the IP3 receptor or mitochondrial calcium uniporter, suggesting that ITPKB acts by negatively regulating the transfer of calcium from the ER into the inner mitochondrial matrix. Importantly, ITPKB knockdown in mouse cortical neurons resulted in increased levels of phosphorylated (Ser129) and insoluble α-synuclein following treatment with α-synuclein preformed fibrils (PFFs). Conversely, overexpression of human ITPKB reduced α-synuclein aggregation induced by PFFs. Taken together, these results implicate ITPKB as a critical mediator of intracellular calcium homeostasis that functions to inhibit α-synculein pathophysiology in PD. Enhancement of ITPKB kinase activity or expression may represent a novel therapeutic strategy for the treatment of sporadic PD.

T22. Characterization of Neural Progenitor/Stem Cell Monolayer and Neurosphere Cultures From Adult Brain Tissue

Raeden Gray, Scarlyn De Los Santos, Elizabeth Batsel, Martin Oudega, Jeffery Plunkett*

Adult zebrafish (Danio rerio) have been shown to retain multiple proliferative neurogenic and stem cell niches to enable growth and repair of central nervous system (CNS) tissues. We initially developed monolayer cellular culture conditions that allowed for the in vitro growth of isolated adult brain cells that contained abundant stem populations. These cultures revealed, at 7 days in vitro (div), the presence of distinct populations of stem cell-derived neural progenitor cells that can differentiate into mature neurons and extend axonal processes. From this data derived in our in vitro monolayer culture, we have more recently developed a free-floating, rotating aggregate culture from adult zebrafish brain. After rotating 5 div, these cultures develop neurospheres of approximately 100-200 micrometers in size and express the stem progenitor and neural progenitor markers Sox2 and NeuroD1. We are currently using a combination of immunocytochemical and statistical analyses to further characterize our neurospheres with an eventual experimental goal of transplantation into the adult brain following CNS trauma.

T23. Analysis of Putative Stem and Neural Progenitor Cell Populations Following Traumatic Brain Injury in Adult Zebrafish

Melanie Rojas Hammani, Taylor Schanel, Martin Oudega, Jeffery Plunkett*

Although post-embryonic neurogenesis is limited in the mammalian brain, zebrafish (Danio rerio) retain multiple proliferative neurogenic and stem cell niches throughout adult life. The focus of our research is to study how traumatic brain injury (TBI) affects the induction of neurogenic progenitor cell fates in the adult zebrafish brain. We hypothesize that TBI will induce an endogenous, quiescent population of progenitor cells that act to integrate and enable the regenerative response seen following injury in the fish. Our data demonstrate prior to injury, the putative stem and neural progenitor markers Sox2, neuroD1 and nestin were expressed around and near ventricular areas of ventral brainstem regions. Furthermore, following 1,3 and 5 days post-TBI, (focal brainstem injury), unilateral migration of stem cells moving out of ventricular areas toward the injury epicenter was observed. These migrating cells displayed an increase in Sox-2, NeuroD1 and PCNA immunoreactivity. We are currently examining these and other time points with the hope to correlate neural-specific gene expression with the migration and differentiation of stem progenitor cells within the injury site.

T24. Functional Magnetic Resonance Imaging as an Objective Evaluation of Patients With Cerebral Palsy After Stem Cell Therapy

David Martinez Garza, Alejandra Garza Bedolla, Ileana Velasco Ruiz, Antonio Valencia Alcocer, Guillermo Elizondo Riojas, Mariana Mercado Flores, Consuelo Mancias Guerra, Olga Graciela Cantu Rodriguez, Cesar Homero Gutierrez Aguirre*

Stem cell-based therapy (SCT) is an alternative for diseases that, until recently, were considered intractable, such as cerebral palsy (CP). Efficacy of SCT has been proven subjectively only through the clinical improvement of the motor and behavioral symptoms of patients with CP. Functional magnetic resonance imaging (fMRI) may be used as a tool that can measure objectively morphological changes that occur in the brain of patient with these interventions.

We present three pediatric patients with severe neurological deficit as consequence of hypoxic-ischemic encephalopathy. They received intrathecal autologous bone marrow (BM) derived total nucleated cells after BM stimulation with granulocyte-colony-stimulating factor, demonstrating improvement of their neuropsychiatric functions. A basal fMRI was obtained and compared with a second fMRI at least 6 months after treatment (figure 1), demonstrating increases on the fractional anisotropy (FA), which

reflects axonal density and myelination in white matter fibers (table 1), which correlated with their clinical improvement. Namely, we measured bihemispheric increases in the corona radiata, the posterior limb of the internal capsule, and the cerebral peduncles.

It has been demonstrated that stem cells are capable of enhancing neurogenesis and angiogenesis in affected hypoxic-ischemic brain tissue. Functional MRI is becoming a powerful tool to evaluate objectively changes occurring in the central nervous system, specifically in the white matter tracts. Randomized studies with control subjects are needed to support this possibility.

T25. Expand Your Mind: Evidence for Psychedelic Enhanced Brain Stimulation

Lucas Dwiel, Alan Green, Wilder Doucette*

Serotonergic psychedelics have recently enjoyed a resurgence in neuroscience and psychiatry with promising success in psychedelic-assisted therapy for the treatment of anxiety, depression, and addiction. The mechanism of action behind this therapeutic effect relies, at least in part, on 5-HT2 agonism which can be negated with the 5-HT2 antagonist, ketanserin. At the cellular level, psychedelics have been shown to increase neuritogenesis, spinogenesis, and synaptogenesis (observed 24 hours after acute administration), effectively priming neural circuits for neuroplasticity, which may help explain the sustained efficacy of psychedelic-assisted therapy. To characterize the therapeutic mechanisms of psychedelics at a neural systems level, the acute drug effects have been described with functional imaging and neural oscillations. Briefly, psychedelics increase the entropy of spontaneous cortical activity, thus relaxing the weight of high-level priors (e.g., beliefs) and allowing for increased bottom-up information flow. However, it appears that the strongest and most reliable therapeutic effects of psychedelics manifest when the drugs are paired with a targeted intervention (e.g., psychotherapy). To better understand this synergistic interaction without human bias, we investigated the effects of LSD alone and paired with deep brain stimulation on neural oscillations in Sprague-Dawley rats. To quantify the difference between brain states we used the accuracy of predictions from models built with the machine learning algorithm Lasso. First, we confirmed prior work showing that acute LSD administration leads to a dramatic shift in neural oscillations compared to controls (AUC = 0.96 vs. 0.83) which disappear within 24 hours, in agreement with the pharmacokoinetics of LSD. Second, although rats given LSD 24 hours previously could not be differentiated from control rats, their brains reacted very differently to deep brain stimulation than controls, suggesting a synergistic effect between psychedelics and a focal intervention that extends beyond the immediate effects of the psychedelic. These results demonstrate that

psychedelics can sensitize, or prime, the brain to future intervention for up to 24 hours – allowing neural activity to be manipulated beyond what is typically possible.

T26. Periaqueductal Gray and Nociceptive Stimulation Activates Ventral Tegmental Area Glutamate Neurons

Leah Pappalardo, Hannah Morgan, Jamie Vizelman, Carlos Mejias-Aponte, Marisela Morales*

The Periaqueductal Gray (PAG) is part of the pain pathway and contains neurons involved in pronociceptive and antinociceptive functions. The PAG sends projections to the Ventral Tegmental Area (VTA), an integral part of the reward pathway. It was recently shown that inactivation of the connection from the PAG to VTA reduces headache-induced conditioned place aversion, suggesting that this projection may encode a component of nociception. Additionally, inactivation of PAG blocks fear conditioning. Our lab has previously shown that VTA glutamate neurons that project to the lateral habenula or to the nucleus accumbens produce conditioned place preference aversion. Therefore, it is possible that the PAG modulation of VTA glutamate neurons may contribute to the perception of pain. To test this hypothesis, we injected Cre-dependent GCaMP6f into the VTA of vGluT2-IRES-Cre transgenic mice and recorded VTA glutamate neuron population responses during stimulation of the PAG and during pain stimulation of the foot pad. We found that the VTA glutamate neurons were excited in response to both stimuli. We are currently confirming these findings by single cell in vivo recordings. This work was funding by the NIDA Intramural Program.

T27. MEF2C Hypofunction in Neuronal and Neuroimmune Populations Produces MEF2C Haploinsufficiency Syndrome Behaviors in Mice

Adam Harrington, Catherine Bridges, Kayla Blankenship, Ahlem Assali, Stefano Berto, Benjamin Siemsen, Hannah Moore, Jennifer Cho, Evgeny Tsvetkov, Acadia Thielking, Genevieve Konopka, David Everman, Michael Scofield, Steven Skinner, Christopher Cowan*

Microdeletions of the MEF2C gene are linked to a syndromic form of autism termed MEF2C haploinsufficiency syndrome (MCHS). Here, we show that MCHS-associated missense mutations cluster in the conserved DNA binding domain and disrupt MEF2C DNA binding. DNA binding-deficient global Mef2c heterozygous mice (Mef2c-Het) display numerous MCHS-like behaviors, including autism-related behaviors, as well as multiple deficits in cortical excitatory synaptic transmission. As a synapse regulator, MEF2C hypofunction in neurons is presumed to underlie MCHS symptoms, but

MEF2C is also expressed in microglia. We find that numerous cortical genes are dysregulated in Mef2c-Hets, including enrichments of autism risk genes, excitatory neuron genes and microglial genes. Interestingly, conditional Mef2c heterozygosity in forebrain excitatory neurons reproduces a subset of the Mef2c-Het phenotypes, while conditional Mef2c heterozygosity in microglia reproduces social deficits and repetitive behavior. Together our findings reveal that MEF2C regulates brain development and function through roles in both neuronal and neuroimmune populations.

T28. Risk of Psychosis in Amphetamine and Methylphenidate Treated Youth: Role of Gender

Matej Markota, Rana Elmaghraby, Paul E. Croarkin, William V. Bobo*

Introduction: There is increasing evidence that youth with attention deficit hyperactivity disorder (ADHD) who are treated with amphetamines are at an increased risk of developing psychosis compared to methylphenidate treated youth. However, only a fraction of youth treated with amphetamines develop psychosis. It is currently unclear if an identifiable subgroup of youth exists that is particularly vulnerable to developing psychosis associated with amphetamine medications. The goal of this study was to test the hypothesis that males are more vulnerable to developing amphetamine medication associated psychosis compared to females. Methods: This was a retrospective, secondary, analysis of a previously developed population-based cohort of Olmsted County (Minnesota, U.S.) residents. All cohort members who were diagnosed with ADHD by 18 years of age and were either treated with amphetamines or methylphenidates, but not both, were included in the final cohort. Cox regression models were used to examine the relationships between treatment and developing any persistent psychotic disorder. Results: Of the 298 youth included in this study (65.4 % male), a total of 18 (6.0%) were diagnosed with a persistent psychotic disorder within 12 years of receiving the first stimulant prescription. Males treated with amphetamines were at a significantly higher risk of developing psychosis compared to methylphenidate treated peers (HR 7.9, 95% CI 1.7-37.2). There was no significant difference in risk of developing psychosis between amphetamine and methylphenidate treated females (HR 0.3, 95% CI 0.03-2.2). Conclusion: Our results replicate the findings of a recent study showing increased risk of developing psychosis in youth treated with amphetamines compared to methylphenidate treated youth. In addition, our study suggests that males may be at a higher risk of amphetamine associated psychosis compared to females.

T29. Time-Delimited Signaling of MET Receptor Tyrosine Kinase Regulates Cortical Circuit Development and Critical Period Plasticity

Shenfeng Qiu, Xiaokuang Ma*

Normal development of cortical circuits, including experience-dependent cortical maturation and plasticity, requires precise temporal regulation of gene expression and molecular signaling. Such regulation, and the concomitant impact on plasticity and critical periods, is hypothesized to be disrupted in neurodevelopmental disorders. A protein that may serve such a function is the MET receptor tyrosine kinase, which is tightly regulated developmentally in rodents and primates, and exhibits reduced cortical expression in autism spectrum disorder and Rett Syndrome. We found that peak of MET expression in developing mouse cortex coincides with the heightened period of synaptogenesis, but is precipitously down-regulated prior to extensive synapse pruning and peak period of cortical plasticity. These results reflect a potential on-off regulatory synaptic mechanism for specific glutamatergic cortical circuits in which MET is enriched. In order to address the functional significance of the 'off' component of the proposed mechanism, we created a controllable transgenic mouse line that sustains MET signaling. Continued MET expression in cortical excitatory neurons disrupted synaptic protein profiles, altered neuronal morphology, and impaired visual cortex circuit maturation and connectivity. Remarkably, sustained MET signaling eliminates monocular deprivation-induced ocular dominance plasticity during the normal cortical critical period; while ablating MET signaling leads to early closure of critical period plasticity. The results demonstrate a novel mechanism in which temporal regulation of a pleiotropic signaling protein underlies cortical circuit maturation and timing of cortical critical period, features that may be disrupted in neurodevelopmental disorders.

T30. A Structural Basis for How Ligand Binding Site Alterations Can Allosterically Regulate GPCR Signaling and Engender Functional Selectivity

David Sibley, Marta Sanchez-Soto, Ravi Kumar Verma, Amy Moritz, Comfort Boateng, Hideaki Yano, R. Benjamin Free, Lei Shi*

Signaling bias is the propensity for some agonists to preferentially stimulate G protein-coupled receptor (GPCR) signaling through one intracellular pathway versus another. While GPCR agonists have been described that selectively activate G proteins or β-arrestins, the molecular mechanisms underlying this biased signaling are not well understood. We recently identified a G protein-biased agonist of the D2 dopamine receptor (D2R) that exhibits impaired β-arrestin recruitment. This signaling bias was predicted to arise from unique

interactions of the ligand with a hydrophobic pocket at the interface of the second extracellular loop and fifth transmembrane segment of the D2R. Here, we show that residue F189 within this pocket (position 5.38 using Ballesteros-Weinstein numbering) functions as a micro-switch for regulating receptor interactions with β-arrestin. As this residue is relatively conserved among class A GPCRs, we constructed analogous mutations within other GPCRs and found that these alterations similarly impaired β-arrestin recruitment while maintaining G protein signaling. To investigate the mechanism of this signaling bias, we used an active state structure of the β2-adrenergic receptor (β2R), to build β2R-WT and β2R-Y199A models in complex with the full β2R agonist BI-167107 for molecular dynamics simulations. These analyses identified conformational rearrangements in β2R-Y199A that propagate from the extracellular ligand binding site to the intracellular surface, resulting in a modified orientation of the second intracellular loop in β2R-Y199A, which is predicted to affect its interactions with β-arrestin. Our findings provide a structural basis for how ligand binding site alterations can allosterically affect GPCR-transducer interactions resulting in biased signaling.

T31. The Effects of NMDA Receptor Partial Agonism on rTMS Motor Plasticity

Joshua Brown, William Devries, Mark George*

Transcranial Magnetic Stimulation (TMS) has transformed the approach to neuropsychiatric illness although many limitations remain. Without a mechanistic understanding of how TMS produces lasting therapeutic changes in the brain, advances will be serendipitous and TMS will only reach a fraction of its potential. There are unlimited combinations of parameters possible in TMS including stimulation intensity, frequency, pulse width, time on and off, patterns, and anatomic location. Moreover, the way each of these parameters affect the brain will change based on brain location, regional cell types, circuits and activity patterns specific to each disorder, and brain state will all determine outcome. It is therefore essential to establish the basic mechanism of TMS effects, so that the explosion of clinically-orientated, hypothesis-driven research may be guided by a mechanistic rationale.

A few early studies suggested TMS may work through synaptic plasticity mechanisms including LTP and LTD. Both of these mechanisms depend on neuronal and NMDA receptor activity. The necessity of this activity has been supported in several mechanistic studies combining pharmacology with patterned (Theta-Burst Stimulation (TBS)) or paired (Paired-associative simulation (PAS), Ischemic Nerve Block (INB)) TMS protocols in humans. However, the conventional form of TMS used over the last decade for treatment-resistant depression, 10 Hz repetitive (r)TMS, has never been tested with pharmacology.

Here, we report the results of a randomized, double-blind, crossover study investigating the sufficiency of NMDA receptor activity by administering d-cycloserine, an NMDA receptor partial agonist, or placebo in 10 Hz rTMS in ten healthy human subjects. We measured plasticity in the motor cortex with motor evoked potentials (MEPs) from electromyography (EMG) before and after rTMS using neurophysiology techniques including: paired pulse methods to isolate intracortical inhibition and intracortical facilitation; singled pulse methods assessing the cortical silent period and recruitment curve, and MEPs over 60 minutes to follow decay over time. The results of this study will help address the critical gap in mechanistic TMS knowledge, and may provide insight into the potential for pharmacologic augmentation of TMS.

T32. Overexpression of the Neural Chaperone ProSAAS Attenuates the Transsynaptic Spread of Synuclein and Improves Parkinson's Symptoms in Rodent Models of PD

Iris Lindberg, Michael Helwig, Hoa Lam, Donato DiMonte, Nigel Maidment*

The proSAAS chaperone is a low molecular weight, abundant secretory protein which is expressed by neurons within the brain. Prior work has demonstrated that proSAAS contains an internal anti-aggregant chaperone domain which blocks the oligomerization of Abeta1-42 and α-synuclein. We have also shown that proSAAS overexpression blocks α-synuclein-induced cytotoxicity in primary cultures of nigral dopaminergic neurons. To assess whether secreted proSAAS can also block α-synuclein spread and protect neuronal function in vivo, we have determined whether virally-mediated proSAAS overexpression can 1) attenuate the transsynaptic spread of α-synuclein; and/or 2) can block motor asymmetry in an α-synuclein overexpression model of Parkinson's disease.

Methods: To examine transsynaptic spread, we administered α-synuclein AAV into the vagus of mice in the presence of AAVs encoding either GFP or proSAAS. After 6 weeks, we quantified the spread of α-synuclein positive neurites into rostral nuclei using immunohistochemistry; this assessment was carried out blinded. To examine proSAAS effects on Parkinson's motor symptoms, we administered either proSAAS- or GFP-encoding lentivirus together with a--synuclein AAV unilaterally into the substantia nigra of rats. Motor asymmetry was assessed using a battery of tests (cylinder, forelimb placement and forelimb bracing) across 6 weeks in a double-blind fashion.

Results: We found that there was significantly less spreading of synuclein into the pons and caudal midbrain in mice which received proSAAS AAV as opposed to GFP-encoding AAV. In addition, motor asymmetry was dramatically attenuated in rats receiving AAV α-synuclein together with proSAAS-encoding lentivirus, as compared to those receiving AAV α-synuclein with GFP-encoding lentivirus.

Conclusions: We conclude that proSAAS overexpression is able to blunt the synaptic spread of α-synuclein from the vagus into other brain regions, suggesting that this chaperone may naturally function in the intrasynaptic space. Further, intranigral overexpression of proSAAS exerted a profound protective effect in a rat Parkinson's model. We hypothesize that the marked improvement in motor skills resulting from nigral proSAAS expression is due to its protective effects on the catecholaminergic nigral-striatal pathway.

WEDNESDAY, JANUARY 29, 2020 • 3:30 P.M. - 4:30 P.M. • JEFFERSON/MADISON

W1. Heterogeneity in Ventral Striatal Subregion Encoding of Reward Taking and Seeking

Katherine Wright, Jennifer Teixeira, Daniel Wesson*

The ability to execute goal-directed behavior requires the coordination of sensory inputs with motivational states. The ventral striatum serves as a site of convergence from cortical and midbrain dopaminergic inputs to evaluate multimodal sensory stimuli and reward valuation, respectively, to inform and select the appropriate behavior. The ventral striatum is comprised of the nucleus accumbens (NAc) and the olfactory tubercle (OT). The NAc is well-established for its role in motivation to take and seek out reinforcing compounds, and recent work from our lab has established the OT's representation of goal-directed behavior and reward value. However, no evidence exists for the role of the OT in reward taking and seeking. Therefore, the overall goal of this study is to distinguish between NAc and OT encoding of reward-taking and reward-seeking. To do this, we acquired multi-site single-unit activity as C57BL/6J mice engaged in an operant sucrose self-administration task followed by extinction and cue-induced reinstatement. In both the NAc and OT we found populations of neurons whose firing patterns were dynamically modulated upon either or both the instrumental response and the consummatory phases, as well as modulation of firing during reward-seeking behavior. Future work will further investigate the dynamics of these populations of neurons to identify neural representations of different aspects of reinforcement and reward taking and seeking, thereby contributing to a more complete understanding of the ventral striatum and neural systems integral in the reward system.
R01DC014443, R01DA049545 to D.W.

W2. Defining How Information Encoding in D1 and D2 Medium Spiny Neurons in the Nucleus Accumbens Guides Motivated Behavior

Jennifer Zachry, Munir Gunes Kutlu, Patrick Melugin, Liorimar Ramos-Medina, Sophie Halpert, Erin Calipari*

Value-based decision-making is at the core of nearly all motivated behaviors and requires the ability to associate outcomes with specific actions and make adaptive decisions about future behavioral action. Research has focused on outlining the neural circuits that underlie this process and defining how the neural activity within defined cellular subpopulations relates to the execution of adaptive behaviors. At the core of value-based decision-making and reinforcement is the nucleus accumbens (NAc) which is integrally involved in learning, selecting, and executing goal-oriented behaviors. The NAc is a heterogeneous population primarily composed of D1 and D2 medium spiny projection (MSN) neurons that are thought to have opposing roles in behavior with D1 MSNs promoting reward and D2 MSNs promoting aversion. However, currently, our understanding of what these populations encode is largely based on optogenetic studies that activate or inhibit these neuronal populations to define how this promotes or inhibits ongoing behavior. By expressing channelrhodopsin selectively in D1- and D2- populations (using D1-Cre and A2A-Cre mice) in the NAc core, we show that mice will nose poke for optical self-stimulation of both cell types, suggesting D2-MSN activity is not inherently aversive. While optogenetic approaches give some information about how cellular activation can modulate behavior, they eliminate the temporally specific neural activity patterns that encode information in behaving animals. To understand how real-time activity in these populations is linked to behavioral execution, we expressed the genetically encoded calcium indicator (GCaMP6f) within D1 and D2 MSNs coupled with in vivo fiber photometry to record from these cell populations in awake and behaving animals during operant conditioning tasks. Utilizing complex reinforcement schedules that allow dissociation of stimulus value, outcome, cue learning, and action, we show that D1 MSNs respond to the presence and intensity of unconditioned stimuli – regardless of value. Conversely, D2 MSNs respond to a mismatch between what is expected and what is received and thus encode errors in prediction in a value-independent fashion. We provide foundational evidence for the discrete aspects of information that are encoded within these cellular populations.

W3. Chronic Opiate Exposure Alters Mesolimbic Dopamine and Social Behavior

Marc Pisansky, Emilia Lefevre, Sam Hochberger, Patrick Rothwell*

Opiate abuse constitutes a significant public health issue, with overdose mortality rates in the United States approaching ~47k cases annually (Center for Disease Control & Prevention). The abuse liability of opiate drugs has been hypothesized to stem in part from dopamine signaling within the nucleus accumbens (NAc), as well as neuroadaptations throughout the mesolimbic dopamine system. Interestingly, animal studies have reported diverse behavioral and dopaminergic outcomes dependent on the pattern and extent of opiate exposure. Our laboratory has previously found that chronic, continuous morphine administration in mice produces psychomotor tolerance, whereas interruption of this regimen produces psychomotor sensitization. Here, we examined the effects of continuous versus interrupted (via twice-daily naloxone injections) or intermittent (daily morphine injections) opiate exposure on dopamine signaling within the NAc using dLight, a genetically-encoded fluorescent biosensor. In vivo recordings of NAc core dopamine were conducted in male and female mice early and late during continuous or interrupted/intermittent morphine exposure, as well as during acute challenges. Using optogenetics, we furthermore examined the effects of chronic morphine exposure on evoked dopamine release from tegmental terminals in the NAc. Lastly, we evaluated the effects of chronic morphine exposure on social behaviors, namely dyadic social interaction and social novelty. Our findings suggest that different patterns of chronic opiate exposure produce divergent consequences in functioning of the mesolimbic dopamine system and deleterious effects on naturalistic reward behaviors.

W4. Cocaine Extinction Induces Dendritic Spine Alterations in Projection-Specific Subpopulations in the Rat Infralimbic Cortex

Kelle Nett, Sara Romig-Martin, Jason Radley, Ryan Lalumiere*

Prior studies suggest ventral medial prefrontal cortex (mPFC), known as the infralimbic cortex (IL), mediates the extinction and inhibition of cocaine seeking, particularly through projections to the nucleus accumbens (NA) shell. Previous work from our laboratory indicates cocaine self-administration, but not passive receipt of cocaine, induces regressive plasticity within the dorsal mPFC, as indicated by dendritic spine density reductions of pyramidal neurons. These results suggest an intersection between cocaine itself and the learned instrumental behavior in terms of prefrontal plasticity alterations. However, it is unclear whether similar changes occur in the IL and whether extinction training further alters dendritic plasticity in the IL. Moreover, it is unclear

whether behavior affects global dendritic plasticity within the IL or specific subpopulations of projection neurons. To address this issue, Sprague-Dawley rats (250-275 g) received bilateral microinjections of a retrograde adeno-associated virus containing a GFP tag into the NAshell and were implanted with intrajugular catheters. Rats then underwent 2 wks of daily 6 h cocaine self-administration, in which active lever presses produced a cocaine infusion (400 μg/infusion) and light/tone cues. Rats then underwent 2 wks of extinction training (1 h / d), in which active lever presses had no consequence, or 2 wks of homecage withdrawal, prior to being euthanized. We then used an intracellular dye cell-loading technique to fill NA shell-projecting IL pyramidal neurons with Lucifer yellow. Neurons were imaged with 3D confocal imaging followed by deconvolution and analysis using NeuronStudio software. Preliminary results suggest extinction selectively alters dendritic spine density and clustering, specifically in IL→NAshell neurons. These findings point to an important interaction between cocaine self-administration and behavioral encoding that influences structure in a subpopulation-specific manner.

W5. Sex Differences in Behavioral Strategies are Accompanied by Altered Neural Circuit Dynamics in Ventral Tegmental Area to Nucleus Accumbens Projections

Amy Johnson, Suzanne Nolan, Emily Chuang, Jennifer Zachry, Munir Kutlu, Erin Calipari*

Women are more vulnerable than men to a number of psychiatric disease states including depression, anxiety, and substance use disorder; however the large majority of studies in these fields have focused on male subjects making studies understanding how these processes occur in females imperative to women's health. It has been hypothesized that sex differences in neuropsychiatric disorders are manifestations of differences in basic reward processing. Thus, our goal was to understand sex differences in these processes as well as identify the neural basis of these differences. By combining a novel behavioral task – designed to dissociate motivated action from cue learning and valence – with in vivo fiber photometry calcium imaging in the ventral tegmental area (VTA) and nucleus accumbens (NAc) we identified the sex-specific activity signatures that underlie this process. First, we showed that female mice self-administer higher levels of sucrose but acquire negative reinforcement at a slower rate, highlighting the importance of stimulus value in the expression of sex differences in learned behavior. Further, in situations where positive and negative stimuli are presented together, females favor avoiding aversive outcomes over seeking rewards. Interestingly, we did not see sex differences in the activity of the VTA to NAc pathway to the initial exposure to positive (sucrose), negative (footshock), or neutral (random cue) stimuli; however, differences emerged later as animals had successfully acquired each task. Our

results highlight that stimulus specific learning is an important factor in the expression of sex differences and shows the importance of understanding context-specific behavior when making conclusions about sex-specific strategies and their neural control.

W6. Effect of Lateral Hypothalamus Excitotoxic Lesions on the Acquisition of Sign-Tracking Behavior

Cristina Maria Rios, Jonathan Morrow*

Cue-reward associations are critical for developing adaptive responses that promote survival. However, reward-associated cues can sometimes acquire excessive motivational value, resulting in maladaptive behaviors such as those associated with addiction and relapse. Individual differences in Pavlovian conditioned approach (PCA) behavior can be used to disentangle the predictive and motivational properties of associative cues. "Sign-tracking" rats will reliably approach a reward-associated cue and interact with it, indicating that the cue itself has acquired incentive-motivational value for these individuals. In contrast, "goal-tracking" rats direct their conditioned behavior away from the cue and towards the site of impending food reward, indicating that they are using the cue solely as a predictor of the reward, but the cue itself has not acquired motivational value for them. Although these behaviors have been well-characterized, the neurocircuitry responsible for biasing sign- and goal-tracking behavior is not well understood. Sign-trackers show increased c-fos activity in regions like the lateral hypothalamus in response to a reward cue, and blocking orexinergic transmission to the paraventricular nucleus of the thalamus disrupts sign-tracking behavior and motivational salience attribution. Because the lateral hypothalamus is a major source of orexin signaling in this region, we excitotoxically lesioned the lateral hypothalamus of rats and tested the acquisition of sign- and goal-tracking. We found that lesioned rats showed reduced acquisition of sign-tracking behavior compared to sham controls, while goal-tracking was unaffected. These data indicate that lateral hypothalamus activity may play a role in attributing motivational value to reward cues. Further dissection of the neurocircuitry Responsible for biasing these behaviors could provide insight into why some individuals are more vulnerable than others to addiction and other neuropsychiatric disorders.

W7. Investigating the Role of Glucocorticoid Receptor Activation in the Propensity to Attribute Incentive Value to Reward Cues

Sofia Lopez, Youngsoo Kim, Robert Kennedy, Shelly Flagel*

Through associative learning, environmental cues become predictors of relevant stimuli (e.g. food). When such cues, however, are attributed with excessive incentive value they gain inordinate control and elicit aberrant behavior. For example, individuals with addiction often relapse when they encounter drug-associated cues, despite the desire to remain abstinent. Using an animal model that captures individual variation in the propensity to attribute incentive value to cues, we are able to examine the neurobiology that contributes to such psychopathology. Following Pavlovian training, rats may develop either a sign- or goal-tracking response. While both sign-trackers (ST) and goal-trackers (GT) attribute predictive value to a food cue, ST also attribute incentive value. Different brain circuits are engaged in response to the cue in ST vs. GT, with dopamine (DA) in the nucleus accumbens (NAc) necessary for incentive, but not predictive, learning. DA interacts with corticosterone (CORT), a primary regulator of the stress response, to mediate motivated behaviors. CORT acts upon glucocorticoid receptors (GR) and increases NAc DA. Yet, little has been done to investigate DA-CORT interactions in the context of ST and GT. Here we assessed the effect of CORT on sign-tracking and DA during Pavlovian learning. 3 mg/kg of CORT or vehicle was administered (i.p.) to male and female rats prior to Pavlovian conditioning sessions. DA samples were obtained via in vivo microdialysis within the NAc during the first (1) and last (6) sessions. CORT administration resulted in an increase in the acquisition of sign-tracking behavior, and enhanced the conditioned reinforcing properties of a discrete food-cue, but to a different degree and male and female rats. In support of the behavioral findings, we hypothesize that NAc DA will increase in response to CORT. These data highlight a role for CORT in DA-dependent learning processes that are relevant to cue-driven psychopathologies.

W8. CRISPR/Cas9 Editing of Neuropeptide Receptor Signaling Reveals an Extended Amygdala Circuit Mechanism Modulating Alcohol Drinking, Anxiety, and Avoidance

William Giardino, Hiroshi Yamaguchi, Luis de Lecea*

Negative emotional states linked to addiction arise from neuroplasticity within neuronal networks of the hypothalamus and amygdala. These circuits encompass an enormous diversity of cell types that display specialized connectivity patterns and innumerable forms of signaling. Specifically, lateral hypothalamus (LH) neurons containing the neuropeptide Hypocretin (Hcrt;

orexin) profoundly influence arousal (wakefulness) and motivated behavior. I previously identified connectivity between Hcrt-LH neurons and "extended amygdala" neurons of the bed nuclei of stria terminalis (BNST) containing the prototypical stress peptide corticotropin-releasing factor (Crf). I then characterized Hcrt-LH and Crf-BNST neurons as tightly coupled nodes in a stress-promoting circuit, suggesting their involvement in addiction. Here, I investigated Hcrt-LH neurocircuits in free-choice binge alcohol drinking by performing genetically defined physiological monitoring, optical manipulations, and molecular perturbations in neurons of freely-behaving mice. First, I identified Hcrt-LH activation during alcohol withdrawal-enhanced anxiety behavior, and used in vivo Ca2+ recordings to reveal withdrawal-dependent sensitivity of Hcrt-LH neurons to aversive stimuli. I next revealed the necessity of Hcrt for behavioral avoidance driven by Crf-BNST stimulation, and focused on BNST-projecting Hcrt-LH neurons with the hypothesis that BNST Hcrt receptors drive excessive alcohol drinking. We developed a CRISPR/Cas9 gene editing system, finding that disruption of HcrtReceptor1 (hcrtr1) in Crf-BNST neurons reduced alcohol intake, anxiety, and avoidance. These studies advanced prior work by identifying the mechanisms through which LH→BNST circuits promote excessive alcohol consumption. We posit an essential role for Crf-BNST-HcrtR1 signaling in alcohol addiction via negative emotionality and dysregulated hyperarousal. These outcomes have major implications for developing effective strategies to treat addiction.

W9. Rat Self-Administration of Toluene Vapor

Kevin Braunscheidel, Wesley Wayman, Michael Okas, John Woodward*

Inhalants, including volatile organic solvents (e.g. toluene), continue to be one of the most prevalent, and often first substances abused by adolescents. Like other drugs of abuse, toluene affects the function of neurons within key brain reward circuits including the prefrontal cortex, ventral tegmental area and nucleus accumbens. However, preclinical models used to study these toluene-induced adaptations generally employ passive exposure paradigms that do not mirror voluntary patterns of solvent exposure observed in humans. To address this shortcoming, we developed an inhalation chamber containing active and inactive nose pokes, cue lights, flow-through vaporizers, and software-controlled valves to test the hypothesis that rats will voluntarily self-administer toluene vapor. Following habituation and self-administration (SA) training rats achieve vapor concentrations associated with rewarding effects of toluene, and maintain responding for toluene infusions, but not for air infusions. During extinction trials, rats showed an initial burst of drug-seeking behavior similar to that of other addictive drugs and then reduced responding to air SA levels. Responding on the active nose poke recovered during cue-induced

reinstatement but not following a single passive exposure to toluene vapor. The results from these studies establish a viable toluene SA protocol that will be useful in assessing toluene-induced changes in addiction neurocircuitry.

W10. Activation of the Estradiol Receptor, GPER1, Attenuates Preference for Cocaine in Male, but Not in Female Rats

Jacqueline Quigley, Jill Becker*

There are sex differences in susceptibility to addiction. Female rodents are more motivated to take cocaine and acquire a preference for cocaine at lower doses than males. More females also prefer cocaine to natural rewards, compared to males. Research from the Becker Laboratory found that these heightened addiction-like behaviors in females are modulated by estradiol, where estradiol potentiates cocaine-induced dopamine levels in the dorsal striatum (dSTR) and motivation for cocaine. Here we report that estradiol also modulates drug preference and motivation for cocaine in males, but in a way that is different from females. The current study investigated the effects of estradiol receptor (ER) manipulation on the preference for cocaine in male and female rats by administering selective ER agonists or antagonists intra-dSTR. We found that in males, ICI182,780 (ERα/β antagonist; GPER1 agonist) or G1 (GPER1 agonist) blocked preference for 10mg/kg cocaine, as measured by conditioned place preference (CPP). Treatment with G15 (GPER1 antagonist) intra-dSTR enhanced preference for 5mg/kg cocaine in males, control males did not acquire CPP at this dose. Neither ICI nor G1 altered female's CPP for cocaine. These data suggest that GPER1 regulates preference for cocaine in males only. We then investigated potential sex differences in ER expression in the dSTR between male and female rats using qPCR, no significant difference in ERα, ERβ or GPER1 expression between the sexes was found. Our final experiment investigated whether estradiol was being synthesized locally within the dSTR to affect CPP by using an aromatase inhibitor (exemestane) to prevent the synthesis of estradiol from testosterone. Intra-dSTR exemestane had no effect on CPP for cocaine in either sex. These data support the notion that these are sex differences in how ERs alter the rewarding properties of drugs of abuse: enhancing motivation in females while attenuating motivation in males.

W11. Sex Differences in Cholinergic Regulation of Local Nucleus Accumbens Circuit Function Controlling Motivation

Lillian Brady, Jennifer Tat, Jennifer Zachry, Alberto Lopez, Munir Kutlu, Erin Calipari*

Considerable progress has been made toward our understanding of psychiatric disease states over recent years; however, a majority of these studies have primarily focused on male subjects. In psychiatric conditions characterized by abnormalities in motivation and reward processing - such as substance abuse disorder - sex is a critical biological variable and women represent a particularly vulnerable population. The lack of data describing the unique neural circuitry underlying these sexual dimorphisms highlight a critical need for preclinical investigation of reward learning and motivation in female subjects. A variety of factors could be contributing to these sex differences – including estrous cycle dependent ovarian hormone fluctuations - but the precise neurobiological mechanisms underlying these differences in reward and motivation are largely unknown. An essential component of the process that controls motivation and reward-seeking behavior is the mesolimbic dopamine pathway, connecting the ventral tegmental area to the nucleus accumbens (NAc). In the NAc, dopamine is released in a tonic/phasic frequency and is heavily modulated by nicotinic acetylcholine receptors (nAChRs) of the cholinergic system located both on dopamine terminals and on other cellular populations within the NAc. Using fast-scan cyclic voltammetry and site-specific pharmacology we measured subsecond dopamine kinetics in male and female mice in either diestrus (low circulating hormones) or estrus (high circulating hormones) and defined sex-differences in local cholinergic regulation of dopamine release in the NAc. We show a differential effect of the nAChR blocker mecamylamine on presynaptic dopamine release in males and females regardless of cycle stage, suggesting a differential organization of cholinergic regulation of NAc circuitry between the sexes. Together this work will expand our understanding of the sex differences in cholinergic regulation of local NAc circuit function underlying reward learning, aiding in the development of better and more effective pharmacotherapies to counter psychiatric disease states in women.

W12. Beta-Caryophyllene: A Novel Therapeutic Approach for Cocaine Use Disorder

Ewa Galaj, Guo-Hua Bi, Eliot Gardner, Zheng-Xiong Xi*

Cocaine use disorder (CUD) continues to be a serious health problem worldwide. Despite intense research, there is still no FDA-approved medication for it. Recent efforts to discover potential effective therapeutics have focused on the endocannabinoid system because of its identification as a neurobiological

substrate underlying drug addiction. In the last decade, there has been growing interest in beta-caryophyllene (BCP), a volatile phytocannabinoid present in high proportions in cannabis and large numbers of spice and food plants. This dietary additive, which possesses a CB2 receptor agonist profile, has been shown to produce promising therapeutic effects for multiple neuropsychiatric disorders. Surprisingly, a therapeutic potential of BCP in the treatment of drug abuse and addiction has not been explored. Here, using gold standard animal models of drug abuse, we systematically evaluated the potential therapeutic utility of BCP against cocaine-related behaviors. In a series of experiments, we found that BCP attenuated cocaine-enhanced electrical brain-stimulation reward in rats and optogenetic intracranial self-stimulation driven by activation of dopamine (DA) neurons in DAT-cre mice, both outcomes indicating reduced reward efficacy and, by extension, reduced cocaine abuse liability. Intriguingly, when administered systemically or orally, BCP attenuated cocaine self-administration in rats, again demonstrating its ability to reduce cocaine abuse. BCP also reduced drug-primed reinstatement of cocaine seeking and cocaine conditioned place preference, indicative of its preventative effects against relapse. When BCP was substituted for cocaine, rats ceased responding, suggesting BCP itself has low liability abuse. These findings concur with our in vivo microdialysis data showing that BCP alone failed to alter extracellular DA in nucleus accumbens. Our findings suggest that BCP shows exceptional promise as a therapeutic candidate in the treatment of CUD. Importantly, given its good oral bioavailability and the advantage of being an already FDA-approved non-toxic dietary additive, BCP is a valuable candidate for drug repurposing programs in translational medicine.

W13. Ethanol Induced Concentration-Dependent Effects on POMC Neuronal Excitability

Jonna Jackson, Erin Nagy, Lauren Hood, M. Foster Olive*

Alcohol abuse is a worldwide public health concern and leads to an estimated 90,000 alcohol-related deaths in the United States annually. Recent evidence suggests that alcohol may promote its euphoric and motivational effects, in part, by activating the endogenous opioid system. Further supporting the role of the endogenous opioid system in alcohol abuse, one of the most frequently utilized medications for treating alcohol use disorders to date is naltrexone, a broad spectrum opioid receptor antagonist. One particular circuit of the endogenous opioid system consists of pro-opiomelanocortin (POMC) producing neurons in the arcuate nucleus (ArcN) of the hypothalamus, which project heavily to reward-related areas. To identify the physiological effects of ethanol on POMC neurons, we utilized whole cell patch-clamp recordings of POMC neurons from POMC-EGFP mice and bath application of ethanol (5-40 mM) to identify alterations in (1) spontaneous baseline

activity, (2) spike threshold/rheobase, (3) spiking characteristics or (4) intrinsic properties. Using whole-cell electrophysiology, we found that bath application of low concentrations of ethanol (10mM) increased the number of spikes in response to a depolarizing current in a majority of recorded cells. Additionally, in a majority of recorded cells, higher concentrations of ethanol (20-40mM) decreased the number of spikes in response to a depolarizing current. While ethanol changed the number of depolarization elicited spikes in a concentration-dependent manner, compared to control, rheobase was unaffected regardless of ethanol concentration. Additionally, spontaneous POMC activity, measured by spontaneous excitatory post-synaptic potentials (EPSPs) at rest were also unchanged in response to ethanol. Interestingly, 5mM ethanol had no effect on the number of spontaneous EPSPs, but significantly decreased the EPSP amplitude. Together, these results suggest that ethanol has concentration-dependent modulatory effects on POMC neuronal physiology. To our knowledge, these are the first studies to characterize the physiological effects of ethanol on POMC-neurons of the hypothalamus and may lend insight into treating alcohol use disorders.

W14. Modeling Motivation for Alcohol in Humans Using Traditional and Machine Learning Approaches

Erica Grodin, Amanda Montoya, Spencer Bujarski, Lara Ray*

Background: Prolonged alcohol use can result in alcohol use disorder (AUD), a chronic relapsing disorder that is often untreated. Individual variability in the development of AUD likely reflects the interaction between chronic use, as well as biological, psychosocial, and environmental risk factors. It remains unknown what variables are associated with alcohol self-administration (SA) phenotypes, which themselves may reflect risk factors.
Methods: Non-treatment-seeking heavy drinkers (n=67) completed an IV alcohol administration paradigm combining an alcohol challenge and a progressive ratio alcohol SA. Growth curve analysis was used to identify SA phenotypes. Two analyses were conducted identify variables that predicted cluster membership. First, a logistic regression was conducted using a-priori risk factors (sex, family history, and delay discounting). Second, a series of random forest models were run to identify clinical predictors.
Results: Two SA phenotypes were identified: (1) motivated, in which participants continued to work for alcohol throughout the session (n=41); and (2) unmotivated, in which participants exhibited limited motivation to work for alcohol (n=26). In the logistic regression, only delay discounting impulsivity significantly predicted SA phenotype (B=-0.54, SE=0.23, $\chi 2$=5.50, p=0.02). The two most important variables identified by the random forests were phasic craving for alcohol and delay discounting.

Conclusion: Clinical characteristics can predict alcohol SA phenotypes. Higher delay discounting, indicating a preference for smaller, sooner over larger, later rewards, was predictive of motivation to work for alcohol in both approaches. The data-driven approach indicated that greater phasic craving during the challenge was predictive of the motivated phenotype. These results indicate that using data-driven approaches to investigate alcohol motivation represents a promising tool to identify individual vulnerability for the development of AUD.

W15. Targeted Epigenetic Editing in the Amygdala Prevents Adulthood Behavioral Pathology Caused by Adolescent Alcohol

John Bohnsack, Huaibo Zhang, Donna He, Amy Lasek, Subhash Pandey*

Alcohol use disorder (AUD) is a chronic, debilitating psychiatric disease that afflicts 6% of the US population and is responsible for 88,000 deaths per year. Adolescent alcohol consumption increases the risk of developing an alcohol use disorder by 5-7 times and comorbid anxiety. Recent advances in the field have suggested that epigenetics plays an important role in transition from adolescent alcohol consumption to the development of an AUD later in life, however probing the specific behavioral and endophenotype outcomes that arise because of epigenetic dysregulation by adolescent alcohol consumption are still largely unknown.

We recently identified that an enhancer region upstream of the activity-regulated cytoskeleton-associated protein (Arc) gene, the synaptic activity response element (SARE) site, undergoes substantial epigenetic remodeling after adolescent alcohol exposure that persists until adulthood in rodents and humans. We utilized a dCas9-P300 strategy to probe if restoring histone acetylation associated with the Arc SARE site would prevent behavioral changes induced by adolescent exposure.

We exposed adolescent rats to intermittent ethanol then allowed them to mature to adulthood. Infusion of dCas9+sgRNAs in the central nucleus of the amygdala prevented elevated anxiety-like behavior, decreases in Arc expression, and decreased H3K27Ac associated with the Arc SARE site. We observed no off-target effects.

Our results indicate that restoring H3K27Ac at the Arc SARE site prevents anxiety-like behavior and decreased Arc expression. Arc is a critical regulator of synaptic plasticity and has long been known to be a hub gene in controlling changes after AIE that persist until adulthood. This suggests the usefulness of dCas9 strategies for evaluating discrete regions in the epigenome to determine their functional consequences which may lead to the development of better therapeutics for the treatment of early onset alcohol use disorders.

W16. Cell Type Specific Role of HDAC3 Within the NAc in Regulating Cocaine-Induced Plasticity

Rianne Campbell, Yousheng Jia, Joy Beardwood, Lilyana Pham, Agatha Augustysnki, Alberto Lopez, Dina Matheos, Gary Lynch, Marcelo Wood*

Cocaine utilizes mechanisms of synaptic plasticity and transcription within the nucleus accumbens (NAc) to promote drug-seeking behaviors. Recent work from the field demonstrates that this occurs in a cell-type specific manner, often differentially affecting mechanisms of plasticity within the two major output cell types of the NAc: dopamine D1- (D1R) vs D2-receptors (D2R) medium spiny neurons (MSNs)1–3. Consistent with this, activation of D1R- and D2R- MSNs drive opposing behavioral responses to cocaine4. However, it is unclear how cocaine affects epigenetic mechanisms within D1R- vs D2R- MSNs to promote cocaine-associated behaviors5,6. Prior work from our lab demonstrates that cocaine disengages histone deacetylase 3 (HDAC3) within the NAc to promote cocaine-induced gene expression and cocaine-associated memory formation7,8. Here, we have investigated the specific role of HDAC3's deacetylase activity in cocaine-induced behaviors and cellular activity within the NAc8. More specifically, we have observed the expression profile of HDAC3 following cocaine exposure within these two MSN cell types. In addition, we have found that disrupting HDAC3's activity using Cre-dependent viral vectors within D1R-MSNs, but not D2R-MSNs, affects cocaine-induced conditioned place preference. In addition, we have studied the effects of blocking HDAC3 activity on cell-type specific changes in cocaine-induced synaptic plasticity within D1R vs D2R-MSNs. Together, these results illustrate how cocaine alters mechanisms of histone acetylation to induce cell-type specific changes in synaptic plasticity that promote drug-associated behaviors.

W17. Epigenetic Priming Underlies Transcriptional Disruption Linked to Cocaine Relapse

Philipp Mews, Hope Kronman, Aarthi Ramakrishnan, Abner Reyes, Simone Sidoli, Benjamin Garcia, Li Shen, Eric Nestler*

Drug addiction is a major public health crisis that exacts tremendous psychological and financial costs on patients, their families, and society at large. Drugs of abuse, despite their very different chemical structures and initial protein targets, ultimately converge by producing persistent plasticity and long-lasting changes in gene regulation in a central brain region of reward, the nucleus accumbens (NAc). Permanent changes in chromatin structure are hypothesized to underlie the transcriptional dysregulation that characterizes drug addiction; however, there is to date no direct link between drug-induced epigenetic alterations and the aberrant gene regulation that contributes to relapse. A fundamental challenge is to determine which neuronal subtypes are responsible: the NAc is composed of two opposing types of medium spiny

neurons (MSNs), the D1 and D2 dopamine receptor-expressing subtypes, which exhibit dramatic differences in activity and effects on drug reward. Here, we investigated the cocaine-induced changes in chromatin genome-wide by ATAC-seq in the distinct D1 and D2 MSN subtypes, and distinguished immediate versus persistent alterations in combination with unbiased histone modification profiling by mass spectrometry and ChIP-sequencing. We found that chronic cocaine persistently alters striatal chromatin structure, especially in D1 MSNs, involving eviction of the histone variant H2A.Z, a recently identified memory suppressor, at key neuronal genes. Curiously, genome accessibility in D1 MSNs is prominently increased at these 'scarred' genes even after prolonged periods of withdrawal, linked to long-lasting dysregulation of gene expression upon relapse. Together, our studies investigate an emerging view of epigenetic adaptation and gene dysfunction that may contribute to drug addiction, providing novel insight into epigenetic priming as an important mechanism whereby drugs of abuse alter brain function and behavior in lasting ways. Since epigenetic aberrations may be reversible, this mechanistic understanding of chromatin 'scarring' by drugs of abuse could pave the way to novel epigenetic interventions to treat drug addiction.

W18. Endocannabinoid Signaling in a Septohabenular Circuit Regulates Anxiety-Like Behavior

Casey Vickstrom, Xiaojie Liu, Laikang Yu, Shuai Liu, Yan Li, Ying Hu, Cecilia Hillard, Qing-song Liu*

The endocannabinoid (eCB) system can mediate anxiolysis, and exogenous cannabinoid agonists (e.g. Δ9-tetrahydrocannabinol) are frequently used for their anxiolytic effects. However, the neural circuits whereby cannabinoids exert these effects remain incompletely identified. The medial habenula (MHb) is a well-conserved epithalamic structure that is a powerful modulator of anxiety- and mood-related behavior in rodents and zebrafish and has been shown by MRI to be decreased in volume in humans with depression. We report in adult male and female mice that the eCB 2-arachidonoylglycerol (2-AG) is released from neurons of the MHb, and that this eCB release retrogradely suppresses an atypical, excitatory GABAergic synaptic input from the medial septum and nucleus of the diagonal band (MSDB) to the MHb. We show using viral-genetic circuit mapping, optogenetics, and slice electrophysiology that the MSDB sends a direct GABAergic projection to neurons of the ventral MHb. We observed CB1 receptor-dependent depolarization-induced suppression of excitatory GABA currents (DSE-GABA) as well as a CB1 agonist-induced suppression of GABA postsynaptic currents in MHb neurons. Using optogenetics, we show that this occurs at MSDB axon terminals in the MHb. Viral-genetic knockdown of CB1 from MSDB neurons led to anxiety-like behavior in mice and abolished DSE-GABA in the MHb, suggesting that 2-AG regulation of MSDB to MHb

neurotransmission can produce anxiolytic behavioral effects. Thus, we have likely identified a novel circuit mechanism whereby eCBs control anxiety-like behavior.

W19. Psychostimulants Exert Dose Dependent Effects on Frontostriatal Neuronal Signaling

Robert Spencer, Andrea Martin, David Devilbiss, Rick Jenison, Craig Berridge*

The prefrontal cortex (PFC) and extended frontostriatal circuitry play a critical role in higher cognitive function with dysregulation implicated in a variety of behavioral pathologies, including addiction and ADHD. Psychostimulants exert potent dose-dependent cognitive actions. In high doses associated with abuse, these drugs robustly impair PFC-dependent cognition. In contrast, low doses used in the treatment of ADHD, improve PFC-dependent cognition. Currently, our understanding of the neural coding bases for the diverse cognitive actions of psychostimulants are unclear. Thus, we examined the effects of cognition-impairing and cognition-enhancing doses of methylphenidate (MPH) on neuronal spiking activity and local field potential (LFP) power spectral density within the dorsomedial PFC (dmPFC) and dorsomedial striatum (dmSTR) in rats performing a spatial working memory task. Within the dmPFC, a cognition-impairing dose of MPH robustly suppressed the activity of neurons strongly tuned to delay and reward, while activating neurons not tuned to reward delivery. In contrast, in the dmSTR, cognition impairing doses of MPH had no effect on neurons strongly tuned to task events, while robustly increasing firing of neurons not strongly tuned to these events. Thus, cognition-impairing doses strongly decrease the signal-to-noise representation of key task events. Interestingly, cognition improving doses had little impact on task-related firing of neurons in either region.

For LFP spectral density, MPH elicited a complex array of actions that were region-, frequency- and dose-dependent. Interestingly, in the PFC, we saw opposing actions of cognition improving vs. cognition impairing doses of MPH on the ratio of theta power to both beta and gamma power. Specifically, cognition enhancing doses increased while cognition impairing doses suppressed these ratios. These ratios have been previously linked to both cognitive function and PFC dysregulation. Lastly, delay-related PFC-STR coherence in the gamma range was increased selectively by the cognition-impairing dose of MPH.

These observations indicate that the cognition-improving vs. cognition-impairing effects of psychostimulants target unique aspects of frontostriatal neuronal coding.

W20. Striatal Melanocortin-4 Receptor Influences Action/ Habit Balance in Mice

Elizabeth Heaton, Aylet Allen, Lauren Shapiro, Shannon Gourley*

Many neuropsychiatric diseases, including substance use disorder, are characterized, in part, by a failure to flexibly adapt to an ever-changing environment. This lack of behavioral flexibility often results in an overreliance on habitual behavior at the expense of goal-directed action, i.e., habitually using a substance to the detriment of progressing in a career. The dorsomedial striatum (DMS) is essential for maintaining goal-directed behavior – it is active during new task learning, and it is re-engaged when habits are "broken". However, the neuronal factors underlying an organism's ability to flexibly toggle between goal-directed and habit-based behavior are not completely understood. We recently compared gene expression in the DMS between mice that could and could not modify familiar instrumental behaviors. These and secondary confirmation experiments revealed that lower levels of the melanocortin-4 receptor (MC4R) are associated with behavioral flexibility (breaking habits). To identify functional consequences, we used viral-mediated gene silencing to selectively reduce Mc4r in the DMS. Mc4r knockdown facilitated animals' ability to select actions based on their consequences, resulting in increased goal-directed behavior. Thus, reducing MC4R expression in the DMS is sufficient to increase behavioral flexibility in mice. MC4R is well studied in the hypothalamus, where its role in energy homeostasis is well understood, yet comparatively little is known about MC4R function in the striatum, despite robust expression. These results reveal for the first time that striatal MC4R is a key factor in sustaining vs. "breaking" habits, with low levels conferring behavioral flexibility.

W21. The Role of GIRK Signaling in Prefrontal Cortical Regulation of Affect, Cognition, and Stress Pathology: Implications for Therapeutic Targeting

Eden Anderson, Steven Loke, Ben Wrucke, Annabel Engelhardt, Evan Hess, Kevin Wickman, Matthew Hearing*

Imbalance in prefrontal cortical (PFC) pyramidal neuron (PYR) excitation and inhibition is thought to underlie behavioral symptomologies shared across numerous neuropsychiatric disorders, including top-down control of affect and flexible decision-making, that are also observed with chronic unpredictable stress (CUS). We have previously shown that G protein-gated inwardly rectifying potassium (GIRK) channels regulate the output of medial PFC PYR output, however little is known regarding regulation of cortical interneurons or the functional relevance of PFC GIRK signaling in regulation of affect, cognition and cortical dynamics. Using a viral-mediated

(Cre-dependent) approach in mice harboring a 'floxed" version of the Girk1 gene we examined effects of disrupting GIRK1-containing GIRK channel expression in PYR residing in the prelimbic (PrL) and infralimbic (IL) regions of the mPFC. In males, loss of PYR GIRK signaling in the PrL but not IL cortex differentially impacted measures of affect/motivation, and impaired working memory and cognitive flexibility. Preliminary studies indicate that loss of GIRK signaling in PL PYR in females has distinctly different effects on behavior, as does constitutive loss of GIRK1 in parvalbumin expressing neurons (interneurons). Similar deficits in affect and cognition were observed following prolonged exposure to CUS, and that CUS produced a reduction in PrL PYR GIRK signaling akin to viral approaches. Viral- and stress-induced behavioral deficits were rescued by systemic injection of a novel, GIRK1-selective agonist, ML-297. Together, GIRK signaling is critical for optimal mPFC cognitive control. Further, disruption of GIRK signaling may underlie stress-related dysfunction of the mPFC and associated psychopathologies and represent a therapeutic target for treating stress-induced deficits in affect and one of the most consistently documented deficits across neuropsychiatric disorders – impaired cognitive flexibility.

W22. Striatal Dopamine Promotes Cognitive Effort by Amplifying the Benefits Versus the Costs of Cognitive Work

Andrew Westbrook*, Ruben van den Bosch, Jessica Määttä, Lieke Hofmans, Danae Papadopetraki, Roshan Cools, Michael Frank

Stimulants like methylphenidate are increasingly used to treat ADHD-like symptoms, and for cognitive enhancement, but the precise mechanisms of action are unknown. Prior theories have alternately pointed to cortical or subcortical effects and modulation of either dopamine or norepinephrine. In this study, we show that striatal dopamine increases willingness to expend cognitive effort for reward, by amplifying the subjective benefits versus the subjective costs of action. Our study utilized convergent evidence including PET measures of dopamine synthesis capacity, methylphenidate, and sulpiride, a D2 receptor agent, to implicate striatal dopamine, in particular. Gaze patterns reveal that attention to benefit versus cost information also promotes cognitive motivation. Furthermore, both methylphenidate and higher dopamine synthesis capacity increase the effect of benefits on the evidence accumulation process. In addition, we find dynamic effects of gaze on choice, where gaze early in a trial magnifies the influence of attended-versus-unattended information while late gaze instead reflects an emerging preference. These findings help resolve conflicting accounts of how gaze impacts economic decision-making more broadly, beyond decisions about cognitive effort.

W23. MRI-Guided Focused Ultrasound and rAAV2-HBKO Lead to Widespread Expression of Transgene in the Brain

Rikke Kofoed, Kate Noseworthy, Kelly Markham-Coultes, Lisa Stanek, Bradford Elmer, Lamya Shihabuddin, Kullervo Hynynen, Isabelle Aubert*

Disorders of the central nervous system (CNS) such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis have no cure. Gene therapy holds the promise to provide long-lasting clinical benefits for these neurodegenerative disorders following a single administration. However, adeno-associated viral vectors (AAVs), commonly used for gene therapy, do not easily bypass the blood-brain barrier (BBB) and efficient AAVs delivery to the CNS requires either very high doses or invasive surgery. Pioneer work at Sunnybrook has established that MRI-guided focused ultrasound (MRIgFUS) can safely, transiently and non-invasively increase the permeability of the BBB in targeted areas of the brain and spinal cord preclinically; and clinically, in brain regions affected in patients with Alzheimer's disease and ALS.

For gene therapy, MRIgFUS offers the advantage to deliver AAVs, administered intravenously at a relatively low dose, to specific areas of the CNS. Here, we used the AAV2-HBKO, known for its enhanced tissue distribution compared to AAV2, with the goal of increasing the number of transduced cells in MRIgFUS-targeted brain regions. The brain regions selected in mice are relevant to those affected in human with neurodegenerative disorders.

Our results demonstrate that the AAV2-HBKO delivered by MRIgFUS to specific regions of the mouse brain (eg striatum) transduces cells beyond the focal size targeted. In addition, widespread transgene expression was observed through neuronal connections (eg striato-nigral pathway). Transgene expression in off-target areas was also investigated.

Our findings represent a new gene therapy strategy with a single, localized, and non-invasive delivery to the brain resulting in high and long-term transgene expression reaching multiple regions. Future studies will focus on using this approach for expression of therapeutic transgenes in animal models of neurodegenerative diseases and determine its use for scalability to human.

W24. Angiotensin II Signaling Potentiates GABA(A) Receptor Activity of GABAergic Pars Reticulata Projection Neurons

Ratan Singh, Gregory Amberg, Jozsef Vigh*

At least 70% of the synapses formed on midbrain dopaminergic neurons are GABAergic and the axon collaterals of the GABAergic substantia nigra pars reticulata (SNr) projection neurons acts most consistently to inhibit dopaminergic neurons in vivo. Angiotensin II (Ang II) is a well-characterized regulator of cardiovascular function in the periphery but it is also found in

the central nervous system where local concentrations can exceed those found in the circulation. Ang II signaling is known to modulate GABAergic neurotransmission in the median preoptic nucleus, anterior hypothalamus, and dorsolateral periaqueductal grey neurons. Interestingly, Ang II, angiotensinogen and the primary receptors for Ang II, AT1R and AT2R, are widely expressed in ventral mesencephalon, including the SNr in both primates and human brain. However, if Ang II signaling takes place in SNr GABAergic cells and if it can affect GABAergic neurotransmission in dopaminergic cells is not known. Here we present evidence of Ang II signaling in GABAergic pars reticulata projection neurons. We find that Ang II significantly decreases the frequency of evoked firing of SNr projection neurons and increases the amplitude of picrotoxin sensitive GABA(A) receptor mediated inhibitory post synaptic currents (IPSC's). These Ang II mediated effects were attenuated by Ang II type 1 receptor (AT1-R) blocker, Losartan and were also blocked by a general G-protein inhibitor, guanosine 5'-O-(2-thiodiphosphate) (GDP-β-s, 1 mM) in the pipette solution, suggesting a G-protein dependent signaling mechanism in these cells. These results provide, for the first time, evidence of Ang II-mediated potentiation of GABA(A) receptors on SNr GABAergic projection neurons and inhibition of their firing. Since GABAergic SNr projection neurons provide most of the inhibitory input to dopaminergic neurons in the nigra compacta, these data suggest that Ang II signaling in GABAergic cells could potentially disinhibit dopaminergic neurons causing an imbalance between inhibitory and excitatory tone which eventually results in increased dopaminergic cell firing.

W25. Rapid Reprogramming Method Differentiates CuATSM Responders/Nonresponders From ALS Patient Population

Cassandra Dennys-Rivers*, Xiaojin Zhang, Rochelle Rodrigo, Annalisa Hartlaub, Joseph Beckman, Maria Clara Franco, Kathrin Meyer

Patient diversity and unknown disease cause are major challenges for drug development and clinical trial design for ALS. Moreover, the heterogeneity of the ALS patient population is not reflected in the currently available transgenic animal models. Hence, the direct translation of potential therapeutics tested in such models to the clinic has proven difficult. To address this issue, we utilized a rapid reprogramming method to convert skin biopsies from ALS patients into neuronal progenitor cells (NPC). Using induced astrocytes (iAs) differentiated from these NPCs in co-culture with mouse embryonic motor neurons, we have developed an in vitro model of ALS to screen potentially therapeutic compounds. Using this assay, we have screened numerous compounds on multiple sporadic (sALS) and familial (fALS) patient lines. Our data indicate a diverse patient response to different therapeutic agents, suggesting shared pathways of interest between patient subgroups. Here we investigated the

effects of one such compound, CuATSM, on iAstrocyte mediated motor neuron toxicity in both sporadic and familial (mtSOD1 and C9ORF72 patients) lines. We identified responders and nonresponders in co-culture assay for each patient subpopulations. Next, we performed a detailed analysis of the effects of CuATSM on known ALS disease markers (oxidative stress, mitochondrial dysfunction, elevation of stress response systems). We identified one shared parameter in mitochondrial activity present in all ALS patient CuATSM responders, that was nonexistent in nonresponders. Treatment of iAstrocytes with CuATSM restored this disease markeractivity to levels comparable to healthy controls. Together, these findings suggest that patient iAstrocytes can be used to identify both disease modifiers and pathways dysregulated in a given individual. Shared pathways amongst patient responders implicated CuATSM as a potential therapeutic strategy for additional disorders. These results indicate that enhanced understanding of cellular profiles could aid clinicians in determining the best treatment approach for patients in the future.

W26. Pipsqueak AI: A Standardized and Automated Method of Biomarker Quantification in Digital Histology Using Machine Learning

John Harkness, Will O'Keefe, Grant Wade, Kristy Lawton, Allison Coffin, Barbara Sorg*

Quantification of immunofluorescent markers following confocal or fluorescence microscopy often requires manual identification of cells or biomarkers within images. This task is time intensive, difficult, and prone to bias and errors. Unintentional bias and attentional limitations during analysis can underlie poor reproducibility of findings in biomedical research and represents a significant barrier to developing effective medical treatments, and promoting confidence in scientific inquiry. We developed a "beta" software package (https://labs.wsu.edu/sorg/research-resources) designed to improve automation and standardization of image analysis, called "Pipsqueak" (Perineuronal net Intensity Program for the Standardization and Quantification of Extracellular matrix Analysis Kit). Since its publication in 2016, Pipsqueak beta has amassed approximately 1,800 users worldwide who use it to quantify the intensity and number of perineuronal nets and other neural markers in the brain. This technology significantly increases data reliability between image raters and decreases the time required for analysis by more than 100-fold. However, Pipsqueak beta requires high-contrast images in order to automatically identify neurons. Suboptimal conditions, like high background staining, off-target structures, overlapping or clustered biomarkers, and atypical morphologies, can lead to artifacts and consequently to inaccurate results and erroneous conclusions. Here, we used machine learning to tune a U-NET convolutional neural network to accurately detect of three fluorescent

biomarkers (Wisteria floribunda agglutinin, 8-oxo-dG, and parvalbumin) in sections of rat prefrontal cortex. We demonstrate the potential to integrate machine learning capabilities into our Pipsqueak technology to produce an adaptive, high-throughput, biomedical image analysis platform that quickly and accurately identifies biomarker targets. Furthermore, we were able to implement "Pipsqueak AI" onto a touchscreen for direct interface with microscope CMOS camera hardware. Our end goal is to advance the reliability and speed of research findings and clinical diagnoses by making this technology widely available to researchers and clinicians.

W27. A Cav2.3-Kv4.2 Complex Regulates A-Type Voltage Gated K+ Currents in Hippocampal Neurons

Jonathan Murphy*, Lin Lin, Jakob Gutzmann, Jiahua Hu, Ron Petralia, Dax Hoffman

The rapidly inactivating A-type outward K+ current mediated by Kv4.2 regulates action potential repolarization, subthreshold dendritic excitability, and synaptic plasticity in CA1 pyramidal neurons of the hippocampus. The native Kv4.2 channel complex includes auxiliary subunits Dipeptidyl aminopeptidase-like proteins (DPP6) and the K+ channel interacting proteins (KChIPs1-4). Recent evidence suggests that Kv4.2 function in hippocampal neurons is regulated by R-type Ca2+ channel (Cav2.3) Ca2+ entry in a KChIP-dependent manner. However, the molecular nature of this interaction has not been explored. Here we present evidence for a Cav2.3-Kv4.2 binding interaction that underlies Ca2+ regulation of Kv4.2. We first identified Cav2.3 and Kv4.2 as interaction partners in a mass spectrometry screen using Kv4.2 as bait and confirmed the interaction by coimmunoprecipitation, immunofluorescence, and electron microscopy in hippocampal neurons. Additionally, we found C/YFP FRET between Cav2.3 and Kv4.2 and a reduced Kv4.2-GFP FRAP mobile fraction in Cav2.3 knockout mouse neurons to provide further support for an intimate Cav2.3-Kv4.2 interaction. To determine if Cav2.3 binding regulates Kv4.2 function, we measured a Cav2.3-dependent increase in Kv4.2 current (~25%) in the presence of the slow Ca2+ chelator EGTA, while the fast Ca2+ chelator BAPTA reversed this increase. Whole cell current recordings of A-type current in Cav2.3 knockout neurons dendrites revealed a significant decrease in current density (~45%) when compared to wild-type. Taken together, these results support a Cav2.3-Kv4.2 interaction in which a CaV2.3 Ca2+ influx regulates Kv4.2 function in CA1 hippocampal neurons. Ongoing research is aimed at determining how dendrite function is shaped by the Cav2.3-Kv4.2 complex.

W28. Lateral Hypothalamic Fast-Spiking Parvalbumin Neurons Modulate Nociception Through Connections in the Periaqueductal Gray Area

Justin Siemian, Cara Borja, Sarah Sarsfield, Alexandre Kisner, Yeka Aponte*

The lateral hypothalamus (LH) contains a diverse collection of cell types crucial for orchestrating behaviors that facilitate survival. Over the past decade, tremendous progress has been made on new methods that allow systematic characterization of the function and connectivity of these heterogeneous neuronal subtypes. While studies have begun to identify LH circuits that regulate food intake and reward-related behaviors, less attention has been given to the contributions of genetically-identified LH circuits that modulate nociceptive behaviors. Here we examined how lateral hypothalamic neurons that express the calcium-binding protein parvalbumin (PVALB; LH-PV neurons), a small cluster of neurons within the LH glutamatergic circuitry, regulate nociception in mice. Using optogenetics to modulate neuronal activity, we found that photostimulation of LH-PV neurons suppressed nociception to an acute, noxious thermal stimulus, whereas photoinhibition potentiated thermal nociception. Moreover, brain slice electrophysiology recordings using channelrhodopsin (ChR2)-assisted circuit mapping (CRACM) revealed that LH-PV axons form functional excitatory synapses on neurons in the ventrolateral periaqueductal gray (vlPAG). Furthermore, photostimulation of LH-PV axons in the vlPAG suppressed nociception to both thermal and chemical visceral stimuli. Interestingly, antagonism of mu-opioid receptors or CB1 cannabinoid receptors with systemically-administered naltrexone or rimonabant, respectively, did not abolish the antinociception evoked by activation of this LH-PV to vlPAG pathway. Importantly, none of the optogenetic manipulations significantly affected locomotor activity or anxiety-like behavior as measured by the open-field and elevated plus maze tests, suggesting that the role of LH-PV neurons is likely specific to nociception. Similar to our results for these acute pain tests, photostimulation of LH-PV neurons or their axonal projections in the vlPAG also significantly attenuated thermal and mechanical hypersensitivity induced by a model of chronic inflammatory pain. Together, these results directly implicate LH-PV neurons in modulating nociception, thus expanding the repertoire of survival behaviors regulated by LH circuits.

W29. Gut–Brain Modulation of Central Thirst Circuitry Controls Satiation

Chris Zimmerman, Erica Huey, Jamie Ahn, Lisa Beutler, Chan Lek Tan, Seher Kosar, Ling Bai, Yiming Chen, Timothy Corpuz, Linda Madisen, Hongkui Zeng, Zachary Knight*

Satiation is the process by which eating and drinking reduce appetite. For thirst, oropharyngeal cues have a critical role in driving satiation by reporting to the brain the volume of fluid that has been ingested. By contrast, the mechanisms that relay the osmolarity of ingested fluids remain poorly understood. Here we show that the water and salt content of the gastrointestinal tract are precisely measured and then rapidly communicated to the brain to control drinking behaviour in mice. We demonstrate that this osmosensory signal is necessary and sufficient for satiation during normal drinking, involves the vagus nerve and is transmitted to key forebrain neurons that control thirst and vasopressin secretion. Using microendoscopic imaging, we show that individual neurons compute homeostatic need by integrating this gastrointestinal osmosensory information with oropharyngeal and blood-borne signals. These findings reveal how the fluid homeostasis system monitors the osmolarity of ingested fluids to dynamically control drinking behaviour.

W30. The Mechanisms and Functional Consequences of Interhemispheric Plasticity

Emily Petrus, Alan Koretsky*

The ability of the brain to re-organize after amputation or nerve damage mediates recovery. Beneficial adaptations are required to compensate for injury, but maladaptive phenotypes such as phantom limb pain or hyperalgesia can also occur. A hallmark of unilateral loss of sensation in adults is the bilateral recruitment of primary and secondary somatomotor brain regions responding to sensation in the unaffected limb. The unaffected limb can cause activation of the affected limbs' cortical areas. The cellular mechanisms underlying these changes and whether they are adaptive or maladaptive for recovery are not understood.

We have developed an adult mouse model of peripheral denervation by transecting the nerve bundle connecting the whiskers to the brain. These mice mimic clinical phenotypes observed by functional magnetic resonance imaging (fMRI). This perturbation yields dramatic changes in cortical circuitry in primary somatosensory barrel cortex (S1BC). The deprived S1BC is recruited to respond to intact whisker stimulation by strengthening callosal synapses specifically from intact S1BC to layer 5 (L5) principal neurons in deprived S1BC. These neurons are hyperexcitable and have an increase in glutamatergic receptor function.

To determine if additional somatosensory processing areas are also affected by denervation, cells were labeled with retrograde viral tracers and pre- and post-synaptic responses and intrinsic properties in neurons were recorded. Deprived S1BC neurons connected to pain regions such as the anterior cingulate cortex (ACC), or somatomotor areas such as secondary somatosensory cortex (S2) or motor cortex (M1) undergo unique modifications depending on the area to which they project. These changes indicate that there has been a shift in the state of deprived S1BC towards responsiveness to intact whisker stimulation. The output-specific targeting of the callosum should guide the study of behavioral adaptations after these sensory perturbations.

W31. LTD Requires Engagement of Two Distinct Mechanisms for Suppression of CaMKII Synaptic Targeting

Sarah Cook, Ulli Bayer*

Learning, memory, and cognition are mediated by hippocampal long-term potentiation (LTP) and depression (LTD) of synaptic strength. These bi-directional processes require the Ca2+/calmodulin (CaM)-dependent protein kinase II α isoform (CaMKIIα) and its auto-phosphorylation at T286. However, only LTP requires accumulation of CaMKII at dendritic spine-localized excitatory synapses, mediated by binding to synaptic NMDA receptors (NMDARs). During LTD, CaMKII instead targets shaft-localized inhibitory synapses and contributes to inhibitory potentiation. Still, mechanisms regulating this input-specific, bi-directional synaptic targeting of CaMKII remain largely unknown. Here, we explore this differential CaMKII synaptic targeting and find that LTD requires suppression of CaMKII accumulation at excitatory synapses by coincidental engagement of two distinct mechanisms: the death associated protein kinase 1 (DAPK1) and CaMKII T305/306 autophosphorylation (pT305/306). Our lab has previously demonstrated that DAPK1 mediates LTD by making CaMKII/NMDAR binding LTP-specific. We have also shown that T305/306 phosphorylation prevents CaMKII/NMDAR binding, at least in vitro. Thus, we endeavored to examine how these mechanisms regulate CaMKII synaptic targeting during LTD. To study the regulation of CaMKIIa movement during plasticity, we used FingR intrabodies to simultaneously live-image endogenous CaMKIIa and excitatory and inhibitory synapse markers in WT and mutant mouse neurons. Either DAPK1 knockout (KO) or overexpression of a phospho-null mutation of CaMKII T305/306 (T305/6AA) was sufficient to allow accumulation of CaMKII at excitatory synapses during both LTP and LTD. By contrast, only phospho-null T305/6AA, but not DAPK1 KO, was sufficient to suppress LTD-induced CaMKII accumulation at inhibitory synapses. Furthermore, we demonstrate for the first time that T305/306 phosphorylation is indeed

(i) induced by LTDstimuli and (ii) required for normal LTD (but not LTP). Thus, DAPK1 and T305/306 auto-phosphorylation control the LTP vs. LTD bi-directional synaptic targeting of CaMKII.

W32. Biased Modulation of a Ligand-Gated Ion Channel

Riley Perszyk*, Sharon Swanger, Chris Shelley, Alpa Khatri, Gabriela Fernandez-Cuervo, Matthew Epplin, Pernille Bülow, Ethel Garnier-Amblard, Pavan Gangireddy, Gary Bassell, Hongjie Yuan, David Menaldino, Dennis Liotta, Lanny Liebeskind, Stephen Traynelis

Allosteric modulators of ion channels typically alter the transitions rates between conformational states without changing the properties of the open pore. We describe identification of a novel class of positive allosteric modulators of N-methyl D-aspartate receptors (NMDARs) that mediate a calcium-permeable component of glutamatergic synaptic transmission and play essential roles in learning, memory, cognition, as well as neurological disease. EU1622-14 increases agonist potency and channel open probability, slows receptor deactivation, in addition to decreasing both single channel conductance and calcium permeability. The unique functional selectivity of this chemical probe reveals a mechanism for enhancing NMDAR function while limiting excess calcium influx, and shows that allosteric modulators can act as biased modulators of ion channel permeation.

Presenter Disclosures

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SNOWBIRD, UTAH

JANUARY 23-28, 2021