2022 WINTER CONFERENCE ON BRAIN RESEARCH

PROGRAM BOOK

JANUARY 30 – FEBRUARY 4, 2022 · SNOWMASS, CO

WELCOME LETTER

Welcome to the 2022 Winter Conference on Brain Research (WCBR) in Snowmass, Colorado. This is our 54th meeting, and it is a pleasure to offer an outstanding schedule of cutting-edge science and professional development, along with some exciting new elements in education outreach.

We know that the world is ever-changing, but the dramatic challenges we have faced since our last meeting in early 2020 are unparalleled. The evolving COVID pandemic continues to be highly stressful to our community, and the summer of 2020 reignited our awareness of social justice issues in the United States and beyond. Yet out of crisis emerges opportunity. Many people renewed their respect for the power of science to provide innovative solutions to global issues, and many renewed their emphasis on diversity, equity, and inclusion.

Thank you, Winter Brain community, for sticking together through these tough times. You responded to surveys that aided the difficult but appropriate decision to cancel WCBR for January 2021; you joined together for the first-ever WCBR Summer Gathering in August 2021; you re-joined the in-person meeting this week if you could, and I trust that you will provide candid feedback and creative ideas for the meeting on our exit survey and at the Diversity and Inclusion Power Hour on Tuesday. Special thanks to the current Board of Directors for serving an extra year and for contributing in unique ways.

The science of WCBR kicks off with the plenary lecture on Monday morning. It is an honor to welcome as our speaker Dr. Rachel Yehuda, PhD, Professor of Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai. She will share her research on the effectiveness of MDMA-assisted psychotherapy in the treatment of PTSD, as she is contributing to a re-awakening to the potential for psychedelics to resolve intractable mental health conditions. Dr. Yehuda will also speak on the same topic in the public-facing Brain Talk Town Meeting on Tuesday evening, available worldwide for the first time, via Zoom.

As always, the rest of the meeting is filled with outstanding scientific panels and posters, methodological short courses on Monday and Wednesday, and supportive professional development workshops on Monday and Wednesday. Everyone is encouraged to join a new approach to our educational outreach efforts by attending an outreach panel on Monday afternoon and making virtual visits to Aspen High School on Tuesday or Friday. Also be sure to attend the ski race, mountain lunch, business meeting, and special poster session with the top-rated presentations by junior investigators, all on Thursday, as well as the awards ceremony and banquet

continued

WELCOME LETTER

on Friday. Congratulations to this year's Travel Fellows and thanks to the mentors who will meet with them throughout the week. Given the unfortunate COVID- and travel-related cancellations, the conference schedule will be available online and in the conference app, but not printed.

We celebrate the work of two WCBR pioneers this year. Dr. Mark Geyer and three of his proteges will explore their work using cross-species translational models to investigate the psychophysiology, neurobiology, and pharmacotherapy of psychiatric disorders. Dr. Jakie McGinty and two of her trainees will discuss their research on the signaling molecules that regulate activity in reward-related brain circuits during drug intake and withdrawal. These two leaders in our field exemplify the lifelong productivity in science, passion for skiing, and commitment to WCBR that have built and sustained this organization.

WCBR is well known for its networking opportunities – during scientific sessions, on the slopes, après ski, and by the fire. Winter activities abound in Snowmass, and the town of Aspen is easily accessible by bus. As a sign of the times this year, please grab a name badge tag at registration to share your preference for physical distancing, as well as your preferred pronouns. Also remember to nominate yourselves or your colleagues for election to the Board of Directors if you would like to join the leadership of this great group. Stay safe, mask up, engage, and enjoy.

Kyle J. Frantz, Conference Chair
54th Winter Conference on Brain Research
Snowmass, Colorado, January 30 – February 4, 2022

Contents

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WCBR Information Desk and Message Center are at the 1st Floor Registration in the Conference Center at Viewline Resort Snowmass.

The Information Desk hours are as follows:

Sunday, January 30, 2022	12:00 PM – 7:00 PM
Monday, January 31, 2022	7:00 AM – 12:00 PM, 2:00 PM – 7:30 PM
Tuesday, February 1, 2022	7:00 AM – 11:30 AM, 2:30 PM – 7:30 PM
Wednesday, February 2, 2022	7:00 AM – 11:30 AM, 2:00 PM – 7:30 PM
Thursday, February 3, 2022	7:00 AM – 10:00 AM, 3:00 PM – 6:00 PM
Friday, February 4, 2022	7:00 AM – 10:00 AM, 3:00 PM – 6:00 PM

Pick up your badge at the WCBR Information Desk at the 1st Floor Registration Desk in the Conference Center at Viewline Resort Snowmass. If you have purchased guest meal tickets, these will also be available at registration.

Exhibits and Poster Sessions are in Salon A. Beverages are provided from 3:30 p.m. – 4:30 p.m., Monday, January 31st through Thursday, February 3rd. Exhibitor setup is Monday, January 31st, from 1:00 p.m. – 3:00 p.m. All exhibitors should have their materials removed by 10:00 p.m. on Thursday, February 3rd.

POSTER SESSION 1, MONDAY, JANUARY 31ST

Posters can be set up after 1:00 p.m. on Monday.

Posters will be available for viewing from 3:00 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 2, TUESDAY, FEBRUARY 1ST

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 3, WEDNESDAY, FEBRUARY 2ND

Posters must be set up between 8:00 a.m. – 11:30 a.m. on Wednesday.

Posters will be available for viewing from 12:00 p.m. – 7:00 p.m. on Wednesday. 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 Wednesday.

POSTER SESSION 4, THURSDAY, FEBRUARY 3RD

Posters must be set up between 8:00 a.m. – 11:30 a.m. on Thursday.

This is a special session displaying the highest-ranked posters by young investigators. Award certificates 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 Thursday.

Please refer to pages 31-42 for a listing of poster sessions.

BREAKFAST is available to all registered attendees and guests.

Breakfast will be available Monday through Friday from 6:00 a.m. – 8:30 a.m. Breakfast vouchers will be distributed at registration. Guest breakfast vouchers will be required for complimentary breakfast and will be available for purchase and distributed at registration.

Stark's Alpine Grill and Last Chair will have a breakfast buffet available each day. Grab-and-go options are available at First Chair coffee shop. Additional venues with a breakfast buffet will be open throughout the week.

Monday, January 31	Stark's Alpine Grill, First Chair, Last Chair, Vista*, Wanderlust*
Tuesday, February 1	Stark's Alpine Grill, First Chair, Last Chair, Wanderlust*
Wednesday, February 2	Stark's Alpine Grill, First Chair, Last Chair
Thursday, February 3	Stark's Alpine Grill, First Chair, Last Chair, Vista*
Friday, February 4	Stark's Alpine Grill, First Chair, Last Chair, Wanderlust*

**Wanderlust and Vista breakfast locations will be open until 7:30 AM.*

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.

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

PHYSICIANS

In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Winter Conference on Brain Research. 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

Amedco LLC designates this live activity for a maximum of 29.50 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Steven Nieto
Suzanne Nolan
Kirsten Porter-Stransky
Lydia Smith-Osborne
Sarah Stern
Milenna van Dijk, *Ann Kelley Memorial Travel Fellow*
Jennifer Wenzel, *Conan Kornestsky Travel Fellow*
Katie Yoest

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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.

The National Institute on Drug Abuse of the National Institutes of Health under Award Number R13DA01234.
The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CORPORATE SUPPORT

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

INDIVIDUAL SPONSORS AND ORGANIZATIONS

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

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DON'T FORGET TO VISIT THE POSTERS & EXHIBITS

PIONEER AWARDS

For the 54th 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 Monday, January 31st and Wednesday, February 2nd.

MARK GEYER, PH.D.

Mark A. Geyer, Ph.D. is Distinguished Professor of Psychiatry and Neurosciences Emeritus at the University of California San Diego (UCSD) and directs the Neuropsychopharmacology Unit of the VISN 22 Veterans Administration Mental Illness Research, Clinical, and Education Center. He began to ski in Oregon, receiving his BA in biology at the University of Oregon in 1966. Since receiving his Masters at the University of Iowa and his Ph.D. in Psychology at UCSD in 1972, he has focused on basic research addressing psychiatric disorders and the related behavioral and neurobiological effects of psychedelics and other psychoactive drugs.

In 1993, Dr. Geyer co-founded the Heffter Research Institute, which pioneered and supported much of the scientific research that has prompted the exploration of psychedelics as potential therapeutics in humans. He also co-founded the Psychedelics and Health Research Initiative at UCSD, which is exploring the efficacy of psychedelics in the treatment of pain disorders.

Dr. Geyer has published over 470 peer-reviewed papers that have garnered over 56,000 citations and an H-index of 121. He is the lead Series Editor for Current Topics in Behavioral Neurosciences, which has completed 47+ volumes. For four decades, his group has had continuous funding from the National Institutes of Health. Dr. Geyer's research focuses on developing parallel behavioral paradigms in animals and humans for use in psychiatric drug discovery.

He has been an active participant in the WCBR since the mid-1970s, having attended over 21 meetings.

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JACQUELINE F. MCGINTY, PH.D.

Dr. Jacqueline (Jakie) McGinty, Ph.D. is a neuroscientist who has studied the neurobiology of substance use disorders for over 30 years. She received her B.A. in Psychology from Connecticut College in New London, CT and her Ph.D. in Anatomy & Cell Biology from SUNY Downstate in Brooklyn, NY in 1978. She did her postdoctoral training in the neuropsychopharmacology lab of Floyd Bloom, M.D. in the Arthur Vining Davis Center at The Salk Institute in La Jolla, CA.

Her initial faculty appointment was at the East Carolina U School of Medicine in 1983. She developed her NIH NIDA-supported research program there studying psychostimulant effects on opioid peptides in the hippocampus and striatum. She left as a Professor in 1999 to join the nascent Department of Physiology & Neuroscience at the Medical University of South Carolina where she directs the MUSC Brain Research Institute.

At MUSC, she developed a completely different line of research studying the effects of BDNF on prefrontal cortical circuits in animals with a cocaine self-administration and relapse history in collaboration with members of the Neurobiology of Addiction Research Center (NARC) now called the Center for Opioid and Cocaine Addiction (COCA) led by Dr. Peter Kalivas.

Jakie went to her first WCBR as an invited speaker in 1988 at Steamboat Springs, CO where she re-commenced skiing after a 15-year hiatus. Being lucky to share a condo with Conan Kornetsky (and others) that year, she became a loyal annual member of his ski team and credits Conan for improving her form and confidence on the slopes throughout the years.

She has served WCBR as its Treasurer for over 10 years, a job made infinitely easier by WCBR's terrific management team. The friendships Jakie has made in the WCBR connectome over the years are some of the sweetest highlights that have accompanied her career as a neuroscientist.

FEATURED PRESENTER

RACHEL YEHUDA, PH.D.

Rachel Yehuda, PhD, Professor of Psychiatry and Neuroscience, is the Director of the Center for Psychedelic Psychotherapy and Trauma Research. She is also Director of the Traumatic Stress Studies Division at the Mount Sinai School of Medicine which includes the PTSD clinical research program and the Neurochemistry and Neuroendocrinology laboratory at the James J. Peters Veterans Affairs Medical Center.

Dr. Yehuda is a recognized leader in the field of traumatic stress studies. She has authored more than 450 published papers, chapters, and books in the field of traumatic stress and the neurobiology of PTSD. Her current interests include the study of risk and resilience factors, psychological and biological predictors of treatment response in PTSD, genetic and epigenetic studies of PTSD and the intergenerational transmission of trauma and PTSD. She has an active federally-funded clinical and research program that welcomes local and international students and clinicians.

Dr. Yehuda's research on cortisol and brain function has revolutionized the understanding and treatment of PTSD worldwide and has been awarded the renowned Max Planck Institute for Psychiatry (Munich, Germany) 2004 Guest Professorship. The appointment signifies a special recognition of the outstanding research she has been performing in the field of neuroscience in the context of studies on causality of psychiatric disorders over the years. In 2019, Dr. Yehuda was elected to the National Academy of Medicine for her seminal contributions to understanding the psychological and biological impact of traumatic stress.

KEYNOTE

Monday, January 31 from 8:00 a.m. – 9:30 a.m.

A Psychedelic Renaissance in Mental Health

Salon A & B

BRAIN TALK TOWN HALL

Tuesday, February 1 from 7:00 p.m. – 8:30 p.m.

Considering Psychedelic Therapies in Mental Health

Salon B

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:
1. 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;

CODE OF CONDUCT *(continued)*

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

3. sexual harassment, as defined in Section 4;

4. 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;

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

6. 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

CODE OF CONDUCT *(continued)*

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

CODE OF CONDUCT *(continued)*

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 and attending 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 meetings.

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.

SUNDAY, JANUARY 30, 2022

6:00 P.M. – 6:30 P.M.

Welcome Reception for Newcomers, Travel Fellows, and Mentors ● Salon C-E

6:30 P.M. – 7:30 P.M.

Welcome Reception (All are welcome!) ● Salon A-B

MONDAY, JANUARY 31, 2022

6:00 A.M. – 8:30 A.M.

Breakfast at Leisure ● Stark's Alpine Grill, First Chair, Last Chair, Vista**, Wanderlust** ● *Please use your breakfast vouchers at the Viewline and Wildwood breakfast locations prior to arriving at the Conference Welcome. Breakfast will not be provided at the Conference Welcome & Opening Plenary meeting room.*

8:00 A.M. – 9:30 A.M.

Conference Welcome and Plenary Address ● Salon A and B

A Psychedelic Renaissance in Mental Health
Rachel Yehuda

9:45 A.M. – 11:00 A.M.

Pioneer Session #1: Mark Geyer ● Ziegler

Cross-species Approaches to Psychiatric Disorders
Pioneer: Mark Geyer
Chair: Susan Powell
Investigators: Victoria Risbrough, Jared Young

11:00 A.M. – 11:45 A.M.

Panel Chair Training Session ● Ziegler

2:00 P.M. – 3:30 P.M.

Professional Development Session # 1 ● Independence Auditorium

Enhancing Your Pedagogical Toolbox: Lessons From the COVID-19 Pandemic
Michael Stefanik (Chair), Matt Carter, David Barker, Lloyd Fricker, Sybil Stacpoole

3:30 P.M. – 4:30 P.M.

Exhibits and Poster Session I ● Salon A

4:30 P.M. – 6:30 P.M.

Panel ● Independence Auditorium

Subcortical Circuits in Behavioral Flexibility and Sequences*
Elora Williams, Christopher Howard, Jared Smith (Chair)

**Not eligible for CME credit, **Vista and Wanderlust breakfast locations will be open until 7:30 A.M.*

MONDAY, JANUARY 31, 2022, CONTINUED

4:30 P.M. – 6:30 P.M.

Panel ● Salon B

Skiing the Forest for the Trees: Navigating Recent Developments in Synaptic Plasticity
Don Arnold, Kristen Harris, Elva Diaz, Mark Dell'Acqua (Chair)

Panel ● Salon C

In Vitro Models as Tools to Identify Disease Mechanisms and Evaluate Potential Therapies for Neurological and Neurodegenerative Diseases
Sanchita Bhatnagaer, Maria Clara Franco, Laura Ferraiuolo, Cassandra Dennys-Rivers (Chair)

Workshop ● Salon D

High School Neuroscience Outreach: How to Get K-12 Students on the Slopes and Risk Savvy*
Susan Ferguson, Kirsten Porter-Stransky, Christopher Evans (Chair), John Mendelson

Panel ● Salon E

Carving out Striatal Acetylcholine's Contributions to Neurotransmission and Behavior
Julia Lemos, Nicolas Tritsch, Lauren Burgeno (Chair)

**Not eligible for CME credit*

4:30 P.M. – 6:30 P.M.

Panel ● Ziegler

If AUDs are Caused by Inflammation/Neuroimmune Dysregulation, What's the Solution?
Fulton Crews (Co-Chair), Leon Coleman, A Leslie Morrow (Chair), Verica Milivojevic, Lara Ray

6:30 P.M. – 7:00 P.M.

Refreshment Break ● Conference Center Lobby

7:00 P.M. – 8:30 P.M.

Panel ● Independence Auditorium

Resting-State Network Targeting for Treatment-Resistant Depression
Nolan Williams (Chair), Conor Liston, Shan Siddiqi (Pre-Recorded)

Panel ● Salon B

Appetitive-Aversive Influences on Cocaine-Seeking - Possible Convergence on Striatal D2 Neurons
Thomas Jhou (Chair), Jeffrey Parrilla-Carrero, Lauren Dobbs, Peter Vento

Short Course ● Salon C

AAV-Based Gene Therapy for the Central Nervous System
Nicole Paulk, Rikke Kofoed (Pre-Recorded), Kathrin Meyer (Chair)

MONDAY, JANUARY 31, 2022, CONTINUED

7:00 P.M. – 8:30 P.M.

Panel ● Salon D

Neuromodulation of Synaptic Transmission and Basal Ganglia Circuits
Sarah Zych (Chair), Andrew Yee, Raajaram Gowrishankar

Panel ● Salon E

Noise Correlations, Information, and Learning
Daniel Scott (Chair), Chengcheng Huang, Jean-Paul Noel

Panel ● Ziegler

An Introduction to Computational Psychiatry From Different Methodological Approaches
Frederike Petzschner, Oliver Robinson, Peter Hitchcock, Isabel Berwian (Chair)

TUESDAY, FEBRUARY 1, 2022

6:00 A.M. – 8:30 A.M.

Breakfast at Leisure ● Stark's Alpine Grill, First Chair, Last Chair, Wanderlust**

6:30 A.M. – 8:30 A.M.

Board of Directors Meeting (Invitation Only) ● Vista

7:30 A.M. – 9:30 A.M.

Panel ● Independence Auditorium

A Slippery Slope and Converging Circuit Trails for Chronic Pain and Addiction
Matthew Hearing, Claire Manning, Steven Nieto, Monique Smith, Catherine Cahill (Chair)

Panel ● Salon B

Midbrain-Extended Amygdala Dysregulation in Stress and Addiction
Meghan Gallo, Dipanwita Pati (Pre-Recorded), Elizabeth Avegno, Julie Fudge

Panel ● Salon C

The Role of the Endocannabinoid Signaling in Both the Development and Maintenance of Substance Use Disorders
Natalie Zlebnik (Chair), Anissa Bara, Jennifer Wenzel (Co-Chair), Sam Bacharach, Jayme McReynolds

7:30 A.M. – 9:30 A.M.

Panel ● Salon D

Structure, Trafficking, and Function of Glutamate Receptors
Johannes Hell (Chair), Terunaga Nakagawa, Andres Maricq, Roger Nicoll, Françoise Coussen-Choquet

Panel ● Salon E

Path From Short-Term to Chronic mTBI is Paved With Astroglial Tiles---New Insights Into the Evolution of Blast-Related Astrocyte Dysfunction and Pathology
Daniel Perl (Chair), David Priemer, David Cook, Annalisa Scimemi, Greg Elder

Panel ● Ziegler

To Reward Prediction Errors..... and Beyond!
Erin Calipari, Melissa Sharpe (Chair), Paul Phillips (Pre-recorded), Kauê Costa, Kate Wassum

***Wanderlust breakfast location will be open until 7:30 A.M.*

TUESDAY, FEBRUARY 1, 2022, CONTINUED

9:30 A.M. – 10:30 A.M.

Diversity and Inclusion Power Hour ● Ziegler

11:00 A.M. – 11:30 A.M.

Poster Viewing and Pre-Lunch Meet Up ● Salon A

3:00 P.M. – 3:30 P.M.

Data Blitz ● Salon C

3:30 P.M. – 4:30 P.M.

Exhibits and Poster Session II ● Salon A

4:30 P.M. – 6:30 P.M.

Panel ● Independence Auditorium

Data-driven Approaches to Enhancing Diversity, Equity, and Inclusion in STEM
Michael Stefanik (Chair), Veronica Martinez-Acosta, Kyle Frantz, Sade Spencer, Michael Taffe

Panel ● Salon B

The Role of Microcircuits in the Striatum
Veronica Alvarez (Pre-Recorded), Lillian Brady (Co-Chair), Suzanne Nolan (Chair), Jordan Yorgason

4:30 P.M. – 6:30 P.M.

Panel ● Salon C

How Maternal Stress Shapes Offspring Brain Development and Behavior: Integrating Behavioral, Neurobiological, and Molecular Data From Clinical and Preclinical Studies
Milenna van Dijk, Rodrigo Grassi-Oliveira (Pre-Recorded), Christoph Anacker (Chair), Annamaria Cattaneo (Pre-Recorded)

Panel ● Salon D

Insular Cortex: The Island of Mis-Regulated Motivational and Affective States
Frederic Hopf (Pre-Recorded), Sarah Stern, Samuel Centanni (Chair), Melanie Pina (Pre-Recorded)

Panel ● Salon E

Neural Circuit Mechanisms of Psychedelic Action
Yi Zuo (Chair), Alex Kwan, Ju Lu, Cristopher Niell (Co-Chair)

TUESDAY, FEBRUARY 1, 2022, CONTINUED

4:30 P.M. – 6:30 P.M.

Panel • Ziegler

Distributed Orbitofrontal Cortex Circuits Coordinate Adaptive Decision Making
Dan Li (Chair), Christina Gremel, Stephanie Groman, Tony Ye

7:00 P.M. – 8:30 P.M.

Brain Talk Town Hall Meeting • Salon B

Considering Psychedelic Therapies in Mental Health
Rachel Yehuda

DON'T FORGET TO VISIT THE POSTERS & EXHIBITS

WEDNESDAY, FEBRUARY 2, 2022

6:00 A.M. – 8:30 A.M.

Breakfast at Leisure ● Stark's Alpine Grill, First Chair, Last Chair

6:30 A.M. – 8:30 A.M.

Travel Fellow/Mentor Breakfast ● Vista

7:30 A.M. – 9:30 A.M.

Panel ● Independence Auditorium

Epigenomic Approaches to Decoding Neural Circuits and Psychiatric Disorders
Anne West (Chair), Marija Kundakovic, Elizabeth Heller, Hyejung Won

Panel ● Salon B

Sticking a Spork in Opioid Reward, Motivation, and Pain: A Neural Circuit and Sex-Specific View of Factors Influencing Opioid Use and Abuse
Bailey Sarka, Devan Gomez, Suman Guha (Chair)

Panel ● Salon C

Innovative Pharmacotherapeutic Strategies for Treating Psychiatric Disease from Bench to Bedside
Sade Spencer (Chair), Kolter Grigsby, Lara Ray

7:30 A.M. – 9:30 A.M.

Panel ● Salon D

The Role of Chromatin Remodeling in Mental Health and Disease
Iva Zovkic (Co- Chair), Philipp Mews (Chair), Alberto Lopez, Marcelo Wood

Panel ● Salon E

Neural Circuits for Visual Information Processing and Behavior
Huizhong Tao (Chair), Aaron McGee, Sandra Kuhlman, Jason Samonds, Cristopher Niell

Panel ● Wanderlust

Cell Type and Circuit Specific Changes Contributing to Neurodevelopmental and Psychiatric Disorders
Amelia Gallitano (Chair), Robert McCullumsmith, Consuelo Walss-Bass

Panel ● Ziegler

Signaling, Composition and Modulation of Synaptic AMPA Glutamate Receptors
Maria Kurnikova, Daniel Choquet, Olivia Buonarati, Johannes Hell (Chair)

WEDNESDAY, FEBRUARY 2, 2022, CONTINUED

9:45 A.M. – 11:00 A.M.

Pioneer Session # 2: Jakie McGinty • Ziegler

Drugs and Peptides: One Woman's Journey Through the Brain
Pioneer: Jacqueline McGinty
Chair: Matthew Hearing
Investigators: Matthew Hearing, Jamie Peters

11:00 A.M. – 11:30 A.M.

Poster Viewing and Pre-Lunch Meet-Up • Salon A

2:00 P.M. – 3:30 P.M.

Professional Development Session # 2 • Independence Auditorium

The Lifecycle of an NIH Grant Application: From Inspiration to Frustration to Celebration
Lakshmi Devi (Chair), Bradley Cooke, Ryan Lalumiere, Laura O'Dell, Qingchun Tong, Matt Carter, David Barker

3:30 P.M. – 4:30 P.M.

Exhibits and Poster Session III • Salon A

4:30 P.M. – 6:30 P.M.

Panel • Independence Auditorium

Prediction and Treatment of Risk Factors for Suicide
Anil Malhotra (Chair), Anna Van Meter, Caitlin Millett, Colleen Hanlon, Miklos Argyelan

4:30 P.M. – 6:30 P.M.

Panel • Salon B

Dopaminergic Pathways in Adaptive and Maladaptive Behaviors
Ted Hsu, Talia Lerner, Munir Kutlu (Chair), Jennifer Zachry (Co-Chair)

Panel • Salon C

Cortical Mechanisms of Pain Modulation
Matthew Banghart (Chair), Edita Navratilova, William Birdsong

Panel • Salon D

Novel Regulatory Pathways for Neuronal Protein Synthesis
Shannon Farris, Elizabeth Jonas, Sulagna Das, Leonard Kaczmarek (Chair)

Panel • Salon E

Homeostatic Plasticity and Sleep in Autism Spectrum Disorders
Lucia Peixoto, Carolyn Jones, Graham Diering, Stephen Smith (Chair)

Panel • Wanderlust

Peripheral Signals Suggest Central Targets for the Treatment of Drug and Alcohol Addiction
Kyle Frantz(Chair), Laura O'Dell, Lorenzo Leggio (Pre-Recorded), Joshua Brown

WEDNESDAY, FEBRUARY 2, 2022, CONTINUED

4:30 P.M. – 6:30 P.M.

Panel ● Ziegler

Novel Insights into Brain Functions Through Tissue Clearing and Whole-Brain Light-Sheet Imaging
Samuel Centanni, Ashley Cunningham, Alexander Smith (Chair)

6:30 P.M. – 7:00 P.M.

Refreshment Break ● Conference Center Lobby

7:00 P.M. – 8:30 P.M.

Panel ● Independence Auditorium

An Open Science Approach to High Resolution, Comprehensive Atlases of Human Brain Morphology
Marek Kubicki (Chair), Nikos Makris

Short Course ● Salon B

Supervised Machine Learning for the Unsupervised Behavioral Neuroscientist
Ann Kennedy, Simon Nilsson (Chair), Kevin Coffey

7:00 P.M. – 8:30 P.M.

Panel ● Salon C

New Developments on Novel Circuits That Govern Responses to Threat and Safety
Jason Radley (Chair), Heidi Meyer, Ryan Lalumiere

Panel ● Salon D

Neural Activity-Dependent Approaches for Molecular and Cellular Characterization of Neuronal Ensembles in Reward Memories
Marine Salery, James Otis (Chair)

Panel ● Salon E

Linking the Pain Experience to the Body: From the Brain to a Yard Sale of Bodily Systems
Patrick Finan, Robert Edwards, Vitaly Napadow (Chair)

Panel ● Ziegler

Oh, the Places You'll Go*
Elora Williams (Chair), Jared Smith, Drew Duglan, Zoe McElligott

**Not eligible for CME credit*

THURSDAY, FEBRUARY 3, 2022

6:00 A.M. – 8:30 A.M.

Breakfast at Leisure ● Stark's Alpine Grill, First Chair, Last Chair, Vista**

7:30 A.M. – 9:30 A.M.

Panel ● Independence Auditorium

Sex-Differences in Aging From Sleep, Pain, Brain Circuitry and Disease States
Josee Guindon (Chair), Holly Hunsberger, Natalie Ebner, John Lawrence (Co-Chair)

Panel ● Salon B

Bringing Polysubstance Use in From the Cold: Novel Clinical and Pre-Clinical Data on a Neglected Topic
Lara Ray, Lori Knackstedt (Chair), Courtney Wilkinson, Mohamed Kabbaj

Panel ● Salon C

Losing Appetite Over Stress? Circuit Mechanisms Mediating the Reciprocal Interaction Between Emotions and Feeding Behavior
Candice Contet (Chair), Jeffery Dunning, Qingchun Tong, Sarah Stern, Yunlei Yang

7:30 A.M. – 9:30 A.M.

Panel ● Salon D

Establishing Brain-Behavior Relationships With Neuromodulation
Colleen Hanlon, Jonathan Downar, Nolan Williams (Chair), Noah Philip

Panel ● Salon E

Endogenous Opioid Systems: Redundant or Specialized?
Lakshmi Devi (Chair), Ivone Gomes, Manoj Puthenveedu (Pre-Recorded), Elyssa Margolis (Pre-Recorded), Lin Tian

Panel ● Wanderlust

Computational Psychiatry Insights into Dimensional Processes
Frederike Petzschner, Amrita Lamba (Co-Chair), Melissa Sharpe, Peter Hitchcock (Chair)

Panel ● Ziegler

Sex Differences in Dopamine Signaling and Behavior
Brooke Bender, Matthew Wanat (Chair), Jill Becker, Erin Calipari

***Vista breakfast location will be open until 7:30 A.M.*

THURSDAY, FEBRUARY 3, 2022, CONTINUED

10:00 A.M. – 11:30 A.M.

Smitty Stevens Ski Race ● Spider Sabich Race Arena

11:30 A.M. – 1:30 P.M.

Mountain Lunch ● Base Village Conference Center

3:30 P.M. – 4:30 P.M.

Exhibits and Poster Session IV ● Salon A

4:30 P.M. – 6:30 P.M.

Panel ● Independence Auditorium

Function and Dysfunction in the Bed Nucleus of the Stria Terminalis
Joanna Dabrowska (Pre-Recorded), Lindsay Halladay, Zoe McElligott, Katie Yoest (Chair)

Panel ● Salon B

Neural Pathways and Molecular Mechanisms Underlying Relapse Behavior and Drug Craving
Charlotte Bavley, Kathryn Reissner (Chair), Michael Stefanik

4:30 P.M. – 6:30 P.M.

Panel ● Salon C

Central Neural Bases for Normal/Abnormal Hearing and Auditory Behaviors
Li Zhang (Chair), Shaowen Bao (Co- Chair), Qiaojie Xiong, Alfonso Junior Apicella, Patrick Kanold, Fan-Gang Zeng

Panel ● Salon D

Using Human Cells and Tissue to Interrogate Genetic Mechanisms of Risk in Schizophrenia
Thomas Hyde (Chair), Brady Maher, Euan Parnell

Panel ● Salon E

The Role of Intrinsic and Extrinsic Factors on Perineuronal Nets and Associated Neuronal Plasticity
Carol Dannenhoffer (Co-Chair), Katherine Conant, Travis Brown, Amy Lasek (Chair)

Panel ● Ziegler

The Evolution of Neurotrauma Research: Past to Present
Cole Vonder Haar (Chair), Akiva Cohen, Kris Martens, Adam Bachstetter, Audrey Lafrenaye

THURSDAY, FEBRUARY 3, 2022, CONTINUED

6:30 P.M. – 7:30 P.M.

WCBR Business Meeting (All are invited and encouraged to attend!) ● Salon B

7:30 P.M. – 9:30 P.M.

Special Poster Session and Reception ● Salon

FRIDAY, FEBRUARY 4, 2022

6:00 A.M. – 8:30 A.M.

Breakfast at Leisure ● Stark's Alpine Grill, First Chair, Last Chair, Wanderlust**

6:30 A.M. – 8:30 A.M.

Board of Directors Meeting (Invitation Only) ● Vista

7:30 A.M. – 9:30 A.M.

Panel ● Independence Auditorium

Extrasynaptic Proteolysis as a Key to Understanding Physiological and Aberrant Synaptic Plasticity
Leszek Kaczmarek (Pre-Recorded), Katherine Conant, Elizabeth Quinlan (Chair), Iryna Ethell (Pre-Recorded)

Panel ● Salon C

Maladaptive Decision-Making in Health and Disease: Rodent and Human Studies
Donna Calu, Cole Vonder Haar (Chair), Mariya Cherkasova, Jared Young

7:30 A.M. – 9:30 A.M.

Panel ● Salon D

Mechanisms and Alterations in Inhibitory GPCR Signaling
Joseph Lebowitz, Chris Ford (Chair), Kim Neve, Brian Muntean

Panel ● Salon E

Consequences of Alcohol Exposure From Adolescence to Senescence
Fulton Crews (Chair), Victoria Macht, Kati Healey, S. Alex Marshall

Panel ● Ziegler

Black Diamonds to White Lines: Exploring the Effects of Stress on Drug-Seeking Behavior
Kayla Siletti (Chair), Kyle Brown, Jayme McReynolds, Marek Schwendt

***Wanderlust breakfast location will be open until 7:30 A.M.*

FRIDAY, FEBRUARY 4, 2022, CONTINUED

4:30 P.M. – 6:30 P.M.

Panel • Independence Auditorium

Behavioral Responses to Noxious Stimuli: How the Brain Promotes Survival Through Coping Mechanisms
Nicolas Massaly, Michael Baratta, David Barker (Chair), Flavia Barbano (Pre-Recorded)

Panel • Salon C

Novel Neurobiological Mechanisms Underlying Neuronal Maintenance and Degeneration*
Hui Zhang, Caiwei Guo, Yimin Zou, Hui-Chen Lu (Chair), Warren Hirst

Panel • Salon D

Opioid Regulation of Glutamate Signaling and Behavior
Dillon McGovern (Chair), Anna Kruyer, Giuseppe Giannotti

Panel • Salon E

Transcriptomic Tools and Molecular Methods for Neural Circuit Dissection in Nonhuman Primates
Mark Eldridge (Chair), Peter Rudebeck (Co- Chair), William Stauffer, Adriana Galvan (Pre-Recorded), J. Megan Fredericks, Vincent Costa

4:30 P.M. – 6:30 P.M.

Panel • Ziegler

Ascending and Descending the Slopes of Prefrontal Pyramidal Neurons in Addiction
Jacqueline McGinty (Chair), Susan Ferguson (Pre-Recorded), Elizabeth Doncheck, Nicholas Graziane (Pre-Recorded), Saurabh Kokane

6:30 P.M. – 7:30 P.M.

Cocktail Hour • Conference Center Lobby

7:30 P.M. – 11:00 P.M.

Awards Banquet and Dance • Viewline Ballroom (Salon A-E)

**Not eligible for CME credit*

MONDAY, JANUARY 31, 2022

POSTER SESSION I • 3:30 P.M. - 4:30 P.M. • SALON A

M1. Investigating the Effects of Social Housing Conditions on Social Behavior and Stimulated Dopamine Release in the Nucleus Accumbens
Ivette Gonzalez

M2. Evaluating the Role of mGlu3 Receptors in Post-Methamphetamine Motivational and Cognitive Deficits
Cassandra Modrak

M3. Using LabGym to Categorize and Quantify Complex Rodent Behaviors
Carrie Ferrario

M4. A Novel Ph-Sensitive Optical Reporter Reveals Compartmentalized Trafficking of the Dopamine Transporter in Neurons
Pingyue Pan

M5. Pharmacological Manipulation of Kv7 (KCNQ) Channels in Cultured Striatal Neurons Affects Electrophysiological Excitability
Emily Jorgensen

M6. An Atlas of Transcriptionally Defined Cell Types in the Rat Ventral Tegmental Area
Robert Phillips

M7. Epigenome Editing of Nucleus Accumbens Cell Subtype Transcripts Regulated by Fentanyl Abstinence
Makeda Turner

M8. Transcriptomic Adaptations in Emotional and Sensory Brain Nuclei in Perinatal Fentanyl Exposed Rodents
Jimmy Olusakin

M9. Capturing and Profiling Cocaine-Recruited Neuronal Ensembles in the Nucleus Accumbens
Marine Salery

M10. More Than a Gut feeling: Cholecystokinin Afferents to the Nucleus Accumbens Encode Aversion and Modulate Dopamine Transmission
Oliver Culver

M11. The Relationship Between Substance Use, Prior Trauma History, and Risk of Developing Post-Traumatic Stress Disorder in the Immediate Aftermath of Civilian Trauma
Felicia Gould

M12. Neuropixels Recordings Reveal Distributed Signaling of Threat Probability and Threat-Elicited Behaviour Across Rodent Midbrain and Pons
Jasmin Strickland

M13. Live Versus Predatory Threat on Foraging by Bed Nucleus of the Stria Terminalis GABA Neurons
Annie Ly

M14. Psychedelic-Induced Alterations in Central Amygdala Reactivity in Response to an Aversive Stimulus
Devin Effinger

MONDAY, JANUARY 31, 2022

POSTER SESSION I • 3:30 P.M. - 4:30 P.M. • SALON A

M15. Role of Gabaergic Inhibitory Interneurons in the Emergence of V1 Visual Sensory Processing
Manal Salmi

M16. Sex and Age-Based Differences in Tactile Function Loss in Persons With Type 2 Diabetes
Stacey Gorniak

M17. Mice Rapidly Update Timed Behaviors in a Serial Fixed Interval Task
Patrick Simen

M18. Cholinergic Transmission in the Nucleus Accumbens Core Alters the Flexibility of Sign-Tracking Responses
Erica Townsend

M19. Habit Prone Mice Exhibit Compulsive-Like Behavior: Potential Involvement of Orbitofrontal MC4R
Sophie Yount

M20. Investigating the Effect of Differential Striatal Dopamine Projections on Reversal Learning and Immediate Early Gene (IEG) Expression
Rochelle van der Merwe

M21. Transcriptional and Anatomical Diversity of Medium Spiny Neurons in the Primate Striatum
Jing He

M22. Early Life Adversity Diminishes Reward Sensitivity and Slows Reinforcement Learning in Mice
Meghan Gallo

M23. Association of Subcortical Grey-Matter Volumes With Life-Course-Persistent Antisocial Behavior in a Population-Representative Longitudinal Birth Cohort
Christina Carlisi

M24. Conformation-Sensitive Antibodies to Protein Kinase C to Study Opioid Receptor Signaling
Achla Gupta

M25. Inhibitory Co-Transmission From Midbrain Dopamine Neurons Depends on Presynaptic GABA Reuptake
Nicolas Tritsch

M26. An Engineered 3D In Vitro Model of Glial-Mediated Neuroinflammation: Toward Understanding Multicellular Mechanisms Underlying Neurodegenerative Diseases
Sophie Brown

M27. Testing the Brain Maintenance and Cognitive Reserve Hypothesis of Cognitive Aging: Application to Vascular and Metabolic Risk Factors
Bryan Neth

M28. Tau Interactome and Functional Study of AKAP9 I2558M Mutation, Alzheimer's Associated Risk Gene Mutation in African American Cohort
Samuel Hersh

MONDAY, JANUARY 31, 2022

POSTER SESSION I • 3:30 P.M. - 4:30 P.M. • SALON A

M29. Local Synthesis of Estrogen in the Ventral Striatum's Tubular Striatum Regulates the Appetitive Nature of Stimuli
Katherine Wright

M30. Effects of Anesthesia and Oxytocin on Dopamine Signaling in the Rat Dorsal Striatum
David Daberkow

M31. Repetitive Mild Traumatic Brain Injuries Increase Motor Impulsivity but Not Choice Impulsivity and Cause Minor Changes in Glial Pathology in Male Rats
Sarah Wampler

M32. Plasticity of Perisynaptic Astroglia During Ischemia-Induced Spreading Depolarization
Sergei Kirov

M33. The Effect of Mild Traumatic Brain Injury on Orexin Neuron Function
Rebecca Somach

M34. Interactions Between Ceftriaxone and Voluntary Abstinence on Relapse to Cocaine Seeking
Yasmin Padovan-Hernandez

M35. Accelerated Theta Burst Stimulation for Bipolar I and II: Assessing Clinical Changes Pre- and Post-Treatment
Kristin Raj

M36. Unraveling the Mechanisms Tying the Gut Microbiome to Central Nervous System Diseases
Stephen Skolnick

M37. Dynamics of VTA Dopaminergic Neuronal Activity During Sleep
Bibi Sulaman

M38. Does TMS Work Through LTP?
Joshua Brown

M39. Ultrastructural Analysis of GluD1-Cbln1 Signaling in the Spino-Parabrachio-Amygdaloid Pain Pathway
Diane Choi

M40. Estrogen and Serotonin Synergistically Enhance the Release of interleukin-6 and Fractalkine from Murine Macrophages: A Potential Mechanism Underlying Sex Differences in Pain
Taylor Hickman

TUESDAY, FEBRUARY 1, 2022

DATA BLITZ • 3:00 P.M. - 3:30 P.M. • SALON A

1. Chronic Morphine Has Opposing Effects on Opioid Sensitivity of Glutamatergic Thalamo-Striatal and Thalamo-Cortical Terminals
Elizabeth Jaeckel

2. Activation of S1PR1 Signaling in the CNS Drives Cisplatin-Induced Cognitive Impairment
Silvia Squillace

3. Dynorphinergic Control of Amygdalo-Striatal Circuits for Goal-Directed Action
Raajaram Gowrishankar

4. Neuronal PAS Domain Protein 4 (Npas4) Regulates Cocaine-Conditioned Behaviors and Synaptic Transmission in a Cell Type-Specific Manner
Brandon Hughes

POSTER SESSION II • 3:30 P.M. - 4:30 P.M. • SALON A

TU1. The Effects of Monoamine Releasers and Reuptake Inhibitors on Behavior Maintained by Social Reinforcement
Mark Smith

TU2. The Role of Striatal Enkephalin in Modulation of Cocaine Seeking
Kanako Matsumura

TU3. Infralimbic Pyramidal Neuron Activity After an Unreinforced Lever Press is Necessary for Encoding Extinction of Heroin Seeking in Rats
Matthew McGregor

TU4. Compartment-Specific Plasticity in Mesolimbic Dopamine Dynamics Following Contingency Learning
Kirsty Erickson

TU5. Naltrexone Reduces Opioid Choice and Relapse in a Heroin Choosing Subpopulation
Victoria Chang

TU6. Critical Role for Serotonin in Aversive Effects of Cocaine
Thomas Jhou

TU7. Neuroinflammation in the Prefrontal Cortex and Striatum Induced by Repeated Binge-Like Intake of the Synthetic Cathinone Methyledioxypyrovalerone (MDPV): Comparison With Methamphetamine
M. Foster Olive

TU8. Distinct Activity in Reward Neurocircuitry in a Rodent Model of Cocaine-Alcohol Polysubstance Use
Javier Mesa

TUESDAY, FEBRUARY 1, 2022

POSTER SESSION II • 3:30 P.M. - 4:30 P.M. • SALON A

TU9. Examining Social Behavior in a Mouse Model for Fragile X Syndrome
Corinne Kelly

TU10. CCR2 Monocytes Repair Cerebrovascular Damage Caused by Chronic Social Defeat Stress in Mice
Miles Herkenham

TU11. A Comprehensive Ethogram of Rat Behavior Across Pavlovian Fear Discrimination
Amanda Chu

TU12. Effects of 3 Months Reduction in Myostatin Levels: Age and Sex Differences
Sonsoles de Lacalle

TU13. An Instability Mechanism for Frequency Coupling of Mesoscopic Activity in the Hippocampus
Alex Sheremet

TU14. Endocannabinoids Control the Neural Substrates of Interval Timing in the Nucleus Accumbens
Natalie Zlebnik

TU15. Disruption of the Proinflammatory Environmental Milieu by Adolescent Ethanol Exposure Adversely Impacts Adult Hippocampal Neurogenesis and Spatial Navigation in Male and Female Rats
Victoria Macht

TU16. Funcitonal Connectivity in Children and Young Adults With Mild TBI
Rebecca Lundwall

TU17. Step-Wise Disassembly of GABAergic Synapses During Pathogenic Excitotoxicity
Joshua Garcia

TU18. β-Amyloid Deposits in a Young COVID Patients
C. Harker Rhodes

TU19. Nrf2 in the RGCS Modulates Glaucoma Pathogenesis Onset and Severity
Sarah Naguib

TU20. Inverse Neurovascular Coupling Contributes to Positive Feedback Excitation of Vasopressin Neurons in Response to a Systemic Homeostatic Challenge
Javier Stern

TU21. Investigating a Potential Role of Cspgs in Neuronal Differentiation of Cultured Adult Stem Cell Populations
Jeffery Plunkett

TU22. Prior Experience With Behavioral Control Over Stress Facilitates Social Dominance
Gabriel Costanza-Chavez

TU23. Leveraging Transfer Learning for Identification and Quantification of Neuronal Biomarkers in Microscopy Images
John Harkness

TUESDAY, FEBRUARY 1, 2022

POSTER SESSION II • 3:30 P.M. - 4:30 P.M. • SALON A

TU24. Positive and Negative Modulators of NMDA Receptor Function Act via Linker Regions Connecting Agonist Binding to the Channel Gate
Elijah Ullman

TU25. Responding to Predicted and Surprising Foot Shock Outcome in Ventral Pallidum and Nucleus Accumbens Core
Mahsa Moaddab

TU26. ClearScope: Image Large and Small Intact Brains Using Light Sheet Theta Microscopy
Aidan E. Sullivan

TU27. Chronic Morphine has Opposing Effects on Opioid Sensitivity of Glutamatergic Thalamo-Striatal and Thalamo-Cortical Terminals
Elizabeth Jaeckel

TU28. Euphorbia Bicolor Latex Extract Reduces Mechanical Allodynia in a Rat Model of Thermal Injury
Temiloluwa Olaoluwa

TU29. Sex Differences in Stress-Exacerbated Orofacial Pain and Glial Density in Ascending Trigeminal Pain Pathways
Daisy Cantu

TU30. Studying Perinatal Risk Factors for Schizophrenia Using a Sibling Birth Cohort
Matej Markota

WEDNESDAY, FEBRUARY 2, 2022

POSTER SESSION III • 3:30 P.M. - 4:30 P.M. • SALON A

W1. Dopaminergic Systems of the Ventral Striatum's Tubular Striatum and Appetitive Responses to Electronic Cigarette Vapor
Natalie Johnson

W2. Oxytocin Attenuates Alcohol Consumption in a Rat Model of Oxycodone+Alcohol Polysubstance Use
Courtney Wilkinson

W3. Intermittent Cocaine Self-Administration in Rats Has Sex-Specific Effects on Addiction-Like Behaviors: Cue extinction, Habitual and Compulsive Cocaine Seeking, and Motivation
Brooke Bender

W4. Behavioral Disturbances of Emotionality and Alcohol Drinking as a Result of Low Social Rank in C57BL/6J Mice
Lara Hwa

W5. Cell-Type Specific FGF13 Regulation of Cortical Function
Susan Lin

W6. Isoform-Selective PI3-Kinase Inhibition Confers Partial Resilience to Cocaine Cessation-Induced Anxiety-Like Behavior
Britton Barbee

W7. Mitochondrial Gene Ontology Pathways and Transcriptional Regulators Impacted by Cocaine Self-Administration in C57Bl/6 Mice
Cali Calarco

W8. Transcription Factor 4 Coordinates Gene Expression and Dopamine Responses in the Nucleus Accumbens
Nathaniel Robinson

W9. Investigating the Redox Regulation of Histone Deacetylase 5 in Cocaine-Seeking Behavior
Daniel Wood

W10. GABAergic and Glutamatergic Ventral Pallidum Neurons Differentially Encode Motivation for Heroin
Nicholas Fayette

W11. Bidirectional Relationship Between Opioids and Disrupted Sleep
Darrell Eacret

W12. Knock down of Irf8 in Brain Using an ASO Protects against Synapse Loss in a Mouse Model of HIV Associated Neurocognitive Disorder
Fredrik Kamme

W13. Prefrontal Dopamine Interferes With the Protective Effects of Behavioral Control in Females
Connor McNulty

WEDNESDAY, FEBRUARY 2, 2022

POSTER SESSION III • 3:30 P.M. - 4:30 P.M. • SALON A

W14. The Role of Prefrontal-Periaqueductal Gray (PAG) Circuits in Conditioned Fear
Julia Mitchell

W15. Nucleus Accumbens Neuron Subtype Translatomes in Social Stressed Females
Gautam Kumar

W16. Impact of Social Defeat Stress on Microglia-Neuron Interactions in the Nucleus Accumbens
Daniela Franco

W17. Repetitive Transcranial Magnetic Stimulation (rTMS) Treatment With Concurrent Measurement of Salivary Biomarkers in Major Depressive Disorder
Ronald See

W18. Molecular Profiling of the Hippocampus in Children With Autism Spectrum Disorders
Harry Pantazopoulos

W19. Multisensory Predictive Coding in Rodent Posterior Parietal Cortex
Alice Van Derveer

W20. Schema Cells in Orbitofrontal Cortex
Wenhui Zong

W21. Dissociating Dopaminergic and Subthalamic Contributions to Effort-Based Decision Making
Guillaume Pagnier

W22. Hierarchical Clustering Optimizes the Tradeoff Between Compositionality and Expressivity of Task Structures in Reinforcement Learning
Rex Liu

W23. Anterior Cingulate Neurons Signal Valueless Associative Information During Sensory Preconditioning
Evan Hart

W24. Gabaergic and Glycinergic Synaptic Transmission in Respiratory-Controlling Kölliker-Fuse Neurons in Female and Male Rett Syndrome Mice
Jessica Whitaker-Fornek

W25. Development of Medial Prefrontal Cortex Circuitry and its Role in the Maturation of Adaptive Avoidance in Mice
Caitlin Goodpaster

W26. Simultaneous Real-Time Detection of Multiple Neurochemicals at Single Recording Sites Using Carbon-Fiber Microbiosensors Coupled With Voltammetry
Leslie Sombers

WEDNESDAY, FEBRUARY 2, 2022

POSTER SESSION III • 3:30 P.M. - 4:30 P.M. • SALON A

W27. Poster Withdrawn

W28. Changes in Locus Coeruleus Firing Suggest Neuronal Hyperactivity and Coincide With Anxiety-Like Behaviors in Young TGF344-AD Rats
Michael Kelberman

W29. Cholinergic Activation Causes Increases in Brain Neurotrophins and Suppresses Beta Amyloid Accumulation Using Nicotinic Receptors in 5xFAD Mice
David Blake

W30. Cardioprotection Following Myocardial Infarction by Hypothalamic Oxytocin Neuron Activation
David Mendelowitz

W31. Regulator of G-Protein Signaling 14 (RGS14) Alters Behavioral and Pathological Responses Due to Kainic Acid-Induced Status Epilepticus
Nicholas Harbin

W32. A3 Adenosine Agonists: Novel Therapeutics to Prevent Traumatic Brain Injury Induced Cognitive Impairment in Rodents
Monica Goodland

W33. Effects of Psilocin on 5-HT2A L5P Neurons
Gavin Schmitz

W34. Intraparenchymal Administration to the Striatum of a Barcoded AAV Library for the Characterization of CAPSID Tropisms in Rodents and Non-Human Primates
Jared Smith

W35. Simultaneous, Real-Time, Pharmacokinetic and Pharmacodynamic (Behavioral) Measurements of Psychoactive Drugs in the Brains of Awake, Ambulatory Rats
Julian Gerson

W36. Chemogenetic Activation of Intracardiac Cholinergic Ganglia Neurons Reduces the Incidence of Arrhythmias After an Acute Myocardial Infarction
Bridget Alber

W37. A Miniature Kinematic Coupling Device for Mouse Head Fixation
Su Jin Kim

W38. Sleep Deprivation Induces Opposing Effects on Dendritic Spine Remodeling in Amygdala-Hippocampal Memory Circuit
Barbara Gisabella

W39. Divergent Opioidergic Brainstem Pathways That Mediate Pain-Breathing Interaction
Sung Han

THURSDAY, FEBRUARY 3, 2022

POSTER SESSION IV • 3:30 P.M. - 4:30 P.M. • SALON A

TH1. Remifentanil Self-Administration in Mice Promotes Sex-Specific Cortico-Striatal Dysfunction Underlying Deficits in Cognitive Flexibility and Reduced Control Over Drug Taking
Matthew Hearing

TH2. Junk-Food Diet Induced Changes in Nucleus Accumbens Glutamatergic Plasticity and Food-Cue Motivated Behavior
Tracy Fetterly

TH3. Rat Infralimbic Projections to the Nucleus Accumbens Shell Encode Cocaine Extinction Contingencies During Temporally Specific Windows
Kelle Nett

TH4. High Dose THC during Adolescence Increases Behavioral Lability to Stress and Thc Later in Life Linked to Perturbations in Astrocytes
Jacqueline-Marie Ferland

TH5. A Role for Ventral Pallidum Glutamate Neurons in the Effects of Stress on Heroin Sensitization
Carley Miller

TH6. Reelin Protein Marks Cocaine-Sensitive Drd1+ Medium Spiny Neurons and Modulates the Transcriptional and Physiological Response to Dopamine
Kasey Brida

TH7. Neuronal PAS Domain Protein 4 (Npas4) Regulates Cocaine-Conditioned Behaviors and Synaptic Transmission in a Cell Type-Specific Manner
Brandon Hughes

TH8. Prenatal THC Exposure Promotes Transcriptional Network Changes in the Ventral Tegmental Area and Promotes Reward Seeking and Phasic Dopamine Terminal Release in the Adult Rat Offspring
Miguel Lujan

TH9. Novelty-Induced Locomotor Behavior Predicts Heroin Vulnerability in Males While Network-Based Clustering Predicts Vulnerability in Both Sexes
Brittany Kuhn

TH10. Pain Catastrophizing is Associated With Increased Alcohol Cue-Elicited Neural Activity Among Individuals With Alcohol Use Disorder
Steven Nieto

TH11. The Fragile X Mental Retardation Protein Regulates Drug-Related Behaviors via its Function in D1 Receptor-Expressing Cells of the NAC
Jessica Huebschman

TH12. Long-Term Access to Fentanyl Vapor Leads to Compulsive-Like Behaviors in Male and Female Mice
Renata Marchette

THURSDAY, FEBRUARY 3, 2022

POSTER SESSION IV • 3:30 P.M. - 4:30 P.M. • SALON A

TH13. Probing the Function of Neuronal Ensembles in Dorsomedial Prefrontal Cortex During Conditioned Reward Seeking
Roger Grant

TH14. Sex Differences in Cognitive Deficits and Inhibitory Activity by Repeated Methamphetamine Exposure
Monserrat Armenta-Reséndiz

TH15. Within Subject Cross-Tissue Analyses of Epigenetic Clocks in Substance Use Disorder Postmortem Brain and Blood
Brenda Cabrera Mendoza

TH16. Circuit-Specific Endocannabinoid Regulation of Somatostatin Interneurons in the Nucleus Accumbens
Veronika Kondev

TH17. Social Hierarchies Negotiate the Response to Psychosocial Stress in an Adult Female Mouse Model of Depression
Lydia Smith-Osborne

TH18. Cell-Type-Specific Dopamine Signaling in Ventral Hippocampus Tracks Anxiety-Related Behavior
Arthur Godino

TH19. Persistent Fluctuations in Striatal Acetylcholine and Dopamine Signaling: an Opportunity for Offline Learning?
Anne Krok

TH20. Striatal Dopamine Boosts Reinforcement Learning, Controlling for Effects on Working Memory and Cognitive Effort
Andrew Westbrook

TH21. Accumbal D1 and D2 Medium Spiny Neurons Have Distinct but Inter-Dependent Roles in Associative Learning
Jennifer Zachry

TH22. Activity Dynamics in the Central Nucleus of the Amygdala During Habit Formation
Kenneth Amaya

TH23. Dynorphinergic Control of Amygdalo-Striatal Circuits for Goal-Directed Action
Raajaram Gowrishankar

TH24. Activation of S1PR1 Signaling in the CNS Drives Cisplatin-Induced Cognitive Impairment
Silvia Squillace

TH25. The Relationship Between Free Triiodothyronine (FT3) and Performance on the Iowa Gambling Task in Bipolar Disorder: Sex Differences Explored
Caitlin Millett

THURSDAY, FEBRUARY 3, 2022

POSTER SESSION IV • 3:30 P.M. - 4:30 P.M. • SALON A

TH26. Spatially-Restricted Dopamine Signals Evoke Post-Synaptic Responses in Striatal Neurons
Andrew Yee

TH27. Regulation of Kölliker-Fuse Neurons by Co-Release of Noradrenaline and Glutamate From the Locus Coeruleus
Adrienn Varga

TH28. Striatal Fiber Photometry Reflects Primarily Non-Somatic Activity
Alex Legaria

TH29. Somatodendritic Release of Cholecystokinin Modulates Ventral Tegmental Area GABAergic Plasticity
Valentina Martinez Damonte

TH30. Tam Receptors are Modulators of Pathology in Amyotrophic Lateral Sclerosis
Youtong Huang

TH31. High Fat Diet Feeding Disrupts Thermal Responsiveness of AGRP Neurons
Jennifer Deem

TH32. A Novel Intersectional Tool to Study Locus Coeruleus Subpopulations
Alex Hughes

TH33. Integrated Analytic and Machine Learning Framework to Leverage Electrophysiology Datasets in the Data Archive for the Brain Initiative
Rachael Garner

TH34. Opioid Inhibition of Projection-Specific, Respiratory-Related Pontomedullary Neurons
Jordan Bateman

TH35. Functional Connectivity Correlated to Rapid Remission to Intermittent Theta-Burst Stimulation (aiTBS) Therapy for Severe Major Depressive Disorder: Results From a Randomized Controlled Clinical Trial
Azeezat Azeez

TH36. An Optogenetic Stimulation-Based Model of Inflammatory Injury Persistently Enhances the Excitability of Spinal Neurons Targeting the Periaqueductal Gray
Chelsie Brewer

TH37. Neural Basis of Opioid-Induced Respiratory Depression and its Rescue
Shijia Liu

TH38. Subcellular Localization of Schizophrenia Risk Genes Encoding Cav1.2 (CACNA1C) and VIPR2 in Rhesus Macaque Dorsolateral Prefrontal Cortex
Dibyadeep Datta

MONDAY, JANUARY 31, 2022
OPENING PLENARY

PLENARY • 8:00 A.M. - 9:30 A.M. • SALON A & B

A Psychedelic Renaissance in Mental Health
Presenter: Rachel Yehuda

Although much has been learned about the neuroscience of trauma and PTSD in the last few decades, the condition remains difficult to treat. The classic approaches of trauma-focused psychotherapy and pharmacotherapy often result in high drop-out rates or relatively small effects. In 2017, however, the FDA designated MDMA-assisted psychotherapy as a breakthrough treatment for PTSD based on the results of Phase 2 trials. Yet MDMA is considered to be a psychedelic and is still designated by the FDA as a Schedule 1 compound, i.e. with no medical benefit and the potential for harm. In mental health and neuroscience, MDMA – which might be better classified as an entactogen – has generally been portrayed as a drug with dangerous neurotoxic effects. As the tide is turning away from these views, a psychedelic renaissance appears to be in process, particularly as it pertains to the treatment of trauma-related disorders. This plenary presentation will review the rationale for using MDMA-assisted psychotherapy in PTSD and examine data from Phase 2 and Phase 3 trials. The extremely promising results of psychedelic therapies have given rise to numerous investigations attempting to understand the mechanism of action of these treatments, heralding a new era not only for the treatment of conditions like PTSD, but also for investigating the neuroscience of consciousness and the brain. These studies will be described, along with ongoing efforts to understand the potential widespread impact of psychedelic-assisted psychotherapy.

PIONEER SESSION #1

PIONEER SESSION • MONDAY • 9:45 A.M. – 11:00 A.M. • ZIEGLER

Cross-species Approaches to Psychiatric Disorders
Pioneer: Mark Geyer
Chair: Susan Powell
Investigators: Victoria Risbrough, Jared Young

We will discuss basic research focused on the psychophysiology, neurobiology, and pharmacotherapy of psychiatric disorders, addressing mechanisms subserving the effects of antipsychotics, psychostimulants, psychedelics, and entactogens. A major challenge has been to develop translational measures appropriate for cross-species studies of psychiatric disorders and the effects of psychoactive drugs. We have used human and animal studies of startle prepulse inhibition (PPI), habituation, and fear conditioning. We found PPI, habituation, and fear learning deficits in different psychiatric disorders and recapitulated them in animals given drugs or after genetic or developmental manipulations. We also conducted behavioral studies of exploratory behavior in mice, rats, and humans and

developed a battery of cross-species tasks for the assessment of cognitive functions. We have explored the effects of many psychoactive drugs to elucidate mechanisms of action and reveal the roles of specific circuits and receptors in behavioral responses to environmental stimuli and cognitive processes. Most of this basic and clinical research has focused on dimensions of behavior relevant to schizophrenia and bipolar disorder.

PROFESSIONAL DEVELOPMENT SESSION #1

SPECIAL SESSION • MONDAY • 2:00 P.M. – 3:30 P.M. • INDEPENDENCE AUDITORIUM

Enhancing Your Pedagogical Toolbox: Lessons from the COVID-19 Pandemic

Chair: Michael Stefanik

Participants: Matt Carter, David Barker, Lloyd Fricker, Sybil Stacpoole

We will discuss basic research focused on the psychophysiology, neurobiology, and pharmacotherapy of psychiatric disorders, addressing mechanisms subserving the effects of antipsychotics, psychostimulants, psychedelics, and entactogens. A major challenge has been to develop translational measures appropriate for cross-species studies of psychiatric disorders and the effects of psychoactive drugs. We have used human and animal studies of startle prepulse inhibition (PPI), habituation, and fear conditioning. We found PPI, habituation, and fear learning deficits in different psychiatric disorders and recapitulated them in animals given drugs or after genetic or developmental manipulations. We also conducted behavioral studies of exploratory behavior in mice, rats, and humans and developed a battery of cross-species tasks for the assessment of cognitive functions. We have explored the effects of many psychoactive drugs to elucidate mechanisms of action and reveal the roles of specific circuits and receptors in behavioral responses to environmental stimuli and cognitive processes. Most of this basic and clinical research has focused on dimensions of behavior relevant to schizophrenia and bipolar disorder.

MONDAY AFTERNOON PANEL SESSIONS

PANEL • MONDAY • 4:30 P.M. – 6:30 P.M. • INDEPENDENCE AUDITORIUM

Subcortical Circuits in Behavioral Flexibility and Sequences

Chair: Jared Smith

Presenters: Elora Williams, Christopher Howard, Jared Smith

Our brains have the remarkable capacity to enable the performance of complex sequences of actions spanning both space and time in the pursuit of our goals, and to flexibly update behavior when environments change. This panel will discuss key neural circuits supporting action sequences and behavioral flexibility.

Elora Williams first will discuss nigrostriatal dopamine transmission in mice performing learned action sequences. She has discovered a particularly strong suppression of

reward-evoked dopamine that is specific to the complete chunked sequence.
Chris Howard will present findings from examinations of dopamine projections to distinct striatal subregions in behavioral flexibility. He has found that optogenetic activation of ventral and dorsomedial dopamine projections supports rapid updating following action-outcome contingency reversal, whereas dorsolateral striatal dopamine yields more inflexible behavior.
Finally, Jared Smith will close the session with a functional characterization of projections from the claustrum to premotor cortex. He has found that this pathway contributes to aversive learning but is dispensable for basic motor control and appetitive cue discrimination learning.

PANEL • MONDAY • 4:30 P.M. – 6:30 P.M. • SALON B

Skiing the Forest for the Trees: Navigating Recent Developments in Synaptic Plasticity

Chair: Mark Dell'Acqua

Presenters: Don Arnold, Kristen Harris, Elva Diaz, Mark Dell'Acqua

Synapses are the fundamental units of information processing and storage in neuronal circuits. Synaptic plasticity mechanisms, such as long-term potentiation (LTP) and depression (LTD), that regulate the structure and strength of excitatory synaptic connections are fundamental to learning and memory. Synaptic plasticity mechanisms can regulate connection strength by modifying presynaptic function, postsynaptic function, as well as the total number of synaptic contacts between neurons. This panel will address new developments in understanding all three of these aspects of synaptic plasticity. Don Arnold (USC) will present exciting new results using selective plane illumination microscopy imaging of large-scale synaptic connectivity to show that region-specific synapse gain and loss, as opposed to changes in the strength of individual synaptic connections, accompany memory formation in larval zebrafish. Kristen Harris (Univ. Texas) will then present new work using electron-microscopic tomography (EMT) to demonstrate that the density of tightly docked synaptic vesicles is increased and vesicle tethering filaments are shorter with their attachment sites shifted closer to the active zone following LTP. Such pre-synaptic structural changes may increase the number of vesicles in a primed state to facilitate the long-lasting increase in glutamate release probability following LTP. Next, Elva Diaz (UC-Davis) will present new results showing that the AMPA-type glutamate receptor (AMPAR) regulatory protein SynDIG4 controls receptor clustering and endocytosis to establish a reserve pool of intracellular AMPARs that is crucial for supporting potentiation of excitatory synaptic strength. Finally, Mark Dell'Acqua (Univ. Colorado) will present new findings characterizing how disruption of normal LTP/LTD balance by synaptotoxic amyloid beta oligomers is mediated by local, postsynaptic AKAP150-anchored PKA and Calcineurin signaling that controls synaptic incorporation versus removal of Ca2+-permeable AMPARs.

In Vitro Models as Tools to Identify Disease Mechanisms and Evaluate Potential Therapies for Neurological and Neurodegenerative Diseases

Chair: Cassandra Dennys-Rivers

Presenters: Sanchita Bhatnagaer, Maria Clara Franco, Laura Ferraiuolo, Cassandra Dennys-Rivers

Neurological and neurodegenerative diseases are extremely difficult to study as many disorders lack an adequate mouse model to effectively represent patients with diverse genetic backgrounds. This lack of heterogeneity in current mouse models makes it difficult to understand disease mechanisms as well as develop therapeutic strategies that are tailored to patient subpopulations. In this panel we will focus on novel in vitro models to study disease mechanisms and evaluate potential therapeutic approaches. Sanchita Bhatnagar will discuss the development of a microRNA-based therapeutic strategy for Rett syndrome and other X-linked disorders. She has identified microRNA106a (miR106a) as a new epigenetic regulator of X chromosome inactivation through a CRISPR/Cas9-based genetic screen. Maria Clara Franco will discuss the use of human and mouse cell culture models of schwannomas associated to the nervous system tumor disorder Neurofibromatosis type 2 to study the role of redox signaling and tyrosine nitration in tumor development and growth. Her group found that tyrosine nitration induces a metabolic reprogramming that supports schwannoma cell growth. By developing a system for the stoichiometric intracellular delivery of nitrated proteins into Schwann cells, nitrated Heat shock protein 90 was identified as the first nitrated target that supports schwannoma cell survival in culture. Laura Ferraiuolo will discuss precision medicine approaches to stratify patient populations based on in vitro pathological characteristics. Furthermore, the impact of ageing and its role in oxidative stress and nuclear-cytosol transport will be explored. Potential therapeutic approaches to target these mechanisms will also be presented. Cassandra Dennys will discuss the use of direct reprogramming of patient fibroblasts into neuronal progenitor cells (NPCs) to model neurological disorders. Subsequent differentiation of NPCs into induced astrocytes (iAs) identified mitochondrial activity states enabling ALS patient cell line subgrouping into responders and nonresponders to CuATSM. These markers were then utilized to repurpose CuATSM mediated therapies to treat infant onset seizure disorders.

High School Neuroscience Outreach: How to Get K-12 Students on the Slopes and Risk Savvy

Chair: Christopher Evans

Presenters: Susan Ferguson, Kirsten Porter-Stransky, John Mendelson, Christopher Evans

Most neuroscientists recognize the importance of sharing science with the public. Some participate in K-12 neuroscience outreach efforts such as SfN's Brain Awareness Week or have given one-off presentations at local schools about neuroscience topics or careers. This workshop will share various outreach programs' goals and methods (both virtual and in-person) that have evolved in universities across the country and discuss how to apply a scholarly approach to outreach. The broad aim is increasing neuroscience outreach efforts, discussing integration of structured trainee-led outreach programs into university trainee education, and growing a network of neuroscientists to support Winter Brain's outreach mission. The format of the workshop will be 5-10 min presentations by outreach program leaders from different universities followed by discussion on process, goals, and assessing effectiveness. Dr. Christopher Evans from UCLA will describe a drug neuroscience outreach program that teaches bioscience undergraduates to prepare, deliver and assess presentations/activities about drugs to high school students. Dr. Kirsten Porter-Stransky from WMU School of Medicine will present an outreach program whereby medical students teach neuroscience in local middle schools, and she will discuss the program's related research projects. Dr. Susan Ferguson, who was a past outreach director at WCBR, will describe the considerable outreach efforts that have emanated from the University of Washington and the Addictions, Drug and Alcohol Institute. Dr John Mendelson will discuss how partnerships with patient advocacy foundations and experts in internet marketing can augment neuroscience outreach. The workshop will have flexibility and allow presentations for discussion by others. If you are interested in presenting an innovative outreach program, contact Dr. Evans (cevans@ucla.edu) prior to the meeting. After the presentations we will open the workshop for critical discussion to optimize the WCBR outreach programs and to create an outreach network that can increase university efforts in neuroscience outreach.

PANEL • MONDAY • 4:30 P.M. – 6:30 P.M. • SALON E

Carving out Striatal Acetylcholine's Contributions to Neurotransmission and Behavior

Chair: Lauren Burgeno

Presenters: Julia Lemos, Nicolas Tritsch, Lauren Burgeno

The striatum, the main input nucleus to the basal ganglia, plays a critical role in coordinating reinforcement, motivation, decision-making, movement, and action planning. It is also one of the brain areas with the highest concentration of markers for cholinergic transmission. Striatal acetylcholine tone, which is mainly supplied by a small population of cholinergic interneurons, exerts a powerful influence over neurotransmission and plasticity through actions at various nicotinic and muscarinic receptor subtypes expressed in the striatum. Because cholinergic receptors are present on all striatal cell types as well as on many of the axonal inputs to the striatum, the mechanisms by which acetylcholine can influence striatal physiology, and behavior as a result, are numerous. This complexity, along with historical technical challenges in measuring and manipulating acetylcholine release in vivo have hampered our ability to refine our understanding of how rapid changes in acetylcholine release interact with activity in other striatal circuits to shape behavior. The recent advent of genetically encoded tools enabling both the measurement and manipulation of cholinergic activity with high temporal precision and cholingergic receptor function, has rekindled interest in this research area. In this panel, speakers will present current research highlighting many of the mechanisms by which striatal acetylcholine neurotransmission can influence network function and behavior, with a particular emphasis on interactions between striatal acetylcholine and dopamine. First, Dr. Julia Lemos (University of Minnesota) will discuss how the muscarinic type 5 receptor (M5) modulates striatal dopamine neurotransmission to shape exploration and promote behavioral adaptation. Dr. Nic Tritsch (New York University) will then present work illustrating the temporal relationship between fluctuations of striatal acetylcholine and dopamine across behavioral contexts. Finally, Dr. Lauren Burgeno (Oxford University) will present data highlighting the distinct roles that ventral and dorsal striatal acetylcholine play in shaping reward guided decision making.

PANEL • MONDAY • 4:30 P.M. – 6:30 P.M. • ZIEGLER

If AUDs are Caused by Inflammation/Neuroimmune Dysregulation, What's the Solution?

Chairs: A. Leslie Morrow, Fulton Crews

Leon Coleman, A. Leslie Morrow, Verica Milivojevic, Lara Ray

Recent evidence suggests that alcohol use disorders (AUDs) involve inflammatory and neuroimmune processes that drive alcohol addiction. This panel will review this evidence and explore new data on strategies to overcome pathological inflammatory or neuroimmune signals in AUD.

Dr. Leon Coleman will present various immune pathways involved in AUD and show which specific pathways could be targeted to treat different components of AUD

pathology. He will discuss the roles of Toll-like receptor-7 (TLR7), microglial activation, and extracellular vesicle signaling in AUD and describe how targeting each one may have unique benefits for treatment.

Dr. Leslie Morrow will present evidence that endogenous neuroactive steroids pregnenolone and allopregnanolone block TLR4 and/or TLR7 pathway activation in mouse and human macrophages and brain of alcohol-preferring P rats. She will also show evidence that treatment of humans with intravenous allopregnanolone dramatically reduces the sensitivity of macrophages to immune pathogens, blocking the neuroimmune pathways that are activated in AUDs.

Dr. Verica Milivojevic will show clinical laboratory and treatment data that examined the effects of the neuroactive steroids progesterone, allopregnanolone and pregnenolone on alcohol-related peripheral stress, cognitive and subjective mood responses and alcohol craving and AUD treatment outcomes. Findings indicate that these neuroactive steroids reduce alcohol craving, negative mood and improve cognitive control and normalize stress biology.

Dr. Lara Ray will present progress on the development of ibudilast, a PDE-4 inhibitor, for AUD treatment. She will show effects of ibudilast in a clinical sample of individuals with current AUD on (a) drinking outcomes, (b) subjective craving and mood, (c) neural markers of alcohol cue-reactivity, (d) peripheral markers of inflammation, and (e) central markers of inflammation derived from spectroscopy.

MONDAY EVENING PANEL SESSIONS

PANEL • MONDAY • 7:00 P.M. – 8:30 P.M. • INDEPENDENCE AUDITORIUM

Resting-State Network Targeting for Treatment-Resistant Depression

Chair: Nolan Williams

Presenters: Conor Liston, Nolan Williams, Shan Siddiqi

Repetitive transcranial magnetic stimulation (TMS) is a proven therapy for treatment-resistant depression but is limited in that the exact network target remains unknown. The FDA-approved rTMS target employs rough scalp measurements to approximate the dorsolateral prefrontal cortex, as early investigators lacked the ability to create personalized targets. Over the last decade, it has become clear that the scalp-based methodology results in high variability in the position of the stimulation site. Multiple independent studies have demonstrated that this variability contributes to heterogeneity in antidepressant response. MRI-based neuronavigation enables precise positioning of the TMS coil over a specific brain location, but one must have a neural target that this technology is approximating to. Leveraging neuronavigation requires a specific neural target to apply the therapy. This group will discuss data converging on a network that involves the dorsolateral prefrontal cortex and the subgenual anterior cingulate cortex. Our panel will present data where this DLPFC-sgACC circuit is utilized in a prospective trial of rapid-acting rTMS for depression. We will also describe new circuit-based TMS targets for other neuropsychiatric syndromes, including substance use disorders, post-traumatic

stress disorder, obsessive-compulsive disorder, personality disorders, and traumatic brain injury.

PANEL • MONDAY • 7:00 P.M. – 8:30 P.M. • SALON B

Appetitive-Aversive Influences on Cocaine-Seeking - Possible Convergence on Striatal D2 Neurons

Chair: Thomas Jhou

Presenters: Jeffrey Parrilla-Carrero, Lauren Dobbs, Peter Vento

Cocaine-seeking is likely mediated by interactions of both rewarding and aversive processes, in some cases driven by overlapping circuits. The first two speakers on this panel respectively examine distinct mechanisms by which D2 medium spiny neurons (D2MSNs) in the striatum could influence either cocaine reward or aversion. The third speaker examines how exogenous activation of the rostromedial tegmentum (RMTg) counters cocaine reward to produce enduring reductions in drug-seeking, possibly also via influences on D2 neurons. The panel chair Thomas Jhou will provide introductory comments and will moderate discussion of the three presentations, which are as follows:

Jeffrey Parrilla-Carrero will present data showing a contribution of striatal D2 medium spiny neurons (D2MSNs) to individual differences in innate aversive effects of cocaine. In particular, accumbens D2MSNs in rats with particularly strong avoidance responses to cocaine display increased excitability, greater basal firing, higher glutamatergic synaptic drive, and decreased long-term depression (LTD). These effects are accompanied by greater RhoA activity, while up/down-regulation of RhoA in D2MSNs decreases/increases cocaine-seeking, respectively. Hence, RhoA critically mediates D2MSN excitability and cocaine-seeking.

Lauren Dobbs will discuss the influences of of striatal met-enkephalin (mEnk) in regulating synaptic transmission in the striatum to affect the rewarding and aversive effects of cocaine. Cocaine enhances pre-proenkephalin (PPE) mRNA in the striatum, in turn leading to larger suppression of striatal inhibitory transmission. Pairing cocaine with intra-accumbens mEnk during conditioning facilitates cocaine place preference, while targeted deletion of PPE from D2MSNs attenuates cocaine place preference. However, accumbal knockdown of PPE impair neither cocaine place preference nor aversion. Hence, low striatal mEnk does not exacerbate aversive aspects of cocaine, but increased mEnk following cocaine appears to keep intra-striatal inhibition low and enhance cocaine reward by facilitating striatal output, which may contribute to vulnerability for cocaine abuse.

Peter Vento will discuss RMTg influences on cocaine-seeking. In particular, optogenetic activation of the RMTg during lever press training to self-administer cocaine produces does not produce an acute reduction in drug-seeking. However, after extinction rats that had previously received optogenetic RMTg stimulation show marked reduction in reinstatement to cocaine-conditioned cues. This indicates that RMTg activation during drug-seeking can produce persistent changes in drug-seeking motivation, possibly via influences on D2MSNs discussed by other panelists.

SHORT COURSE • MONDAY • 7:00 P.M. – 8:30 P.M. • SALON C

AAV-Based Gene Therapy for the Central Nervous System

Chair: Kathrin Meyer

Presenters: Nicole Paulk, Rikke Kofoed, Kathrin Meyer

Gene therapy is gaining momentum for the treatment of neurological disorders. This short-course aims to introduce the fundamentals of gene therapy, focusing on adeno-associated viruses (AAVs). Basic knowledge on the properties of AAVs, their production, and the technologies available to allow AAVs to bypass the blood-brain barrier will be provided. Current challenges and novel strategies for non-invasive gene delivery to the brain will be discussed, as well as the use of AAVs for neurological disorders in the clinic. The primary goal of this course is to provide the learners with a better understanding of the AAVs as a vector for gene therapy and how AAVs can be delivered to the brain, where they can express therapeutic transgenes. Dr. Paulk is an expert in AAV biology and production and will provide a general introduction to AAVs. Dr. Kofoed will discuss current strategies available for non-invasive delivery of AAVs to the brain including MRI-guided focused ultrasound and novel AAV capsids. Dr. Meyer is a leader in the field of translational gene therapy and will provide insights into the use of AAVs in the clinic for the treatment of neurological disorders.

PANEL • MONDAY • 7:00 P.M. – 8:30 P.M. • SALON D

Neuromodulation of Synaptic Transmission and Basal Ganglia Circuits

Chair: Sarah Zych

Presenters: Sarah Zych, Andrew Yee, Raajaram Gowrishankar

Neuromodulatory actions on synaptic transmission adjust synaptic strength, regulate neuronal activity, and modify circuit output to shape behaviors. There is a growing appreciation for heterogeneity of anatomically defined circuits and circuit specific modulation within the basal ganglia that contribute to powerful changes in motivated behaviors. In this panel, speakers will discuss recent work examining the circuit and synaptic mechanisms that modulate neurotransmitter release and underlie changes in behavioral output. 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 differentially modulated at striatal synapses. Andrew Yee (University of Colorado) will present work using two-photon microscopy of a genetically-encoded fluorescent dopamine sensor, and electrophysiology to decode dopamine signals in striatal brain slices. Raaj Gowrishankar (University of Washington) will present recent work on the structural and functional heterogeneity of GABAergic and dopaminergic inputs across the dorsoventral axis of the NAc shell and their distinct contributions to rewarding and/or aversive behavioral outcomes.

PANEL • MONDAY • 7:00 P.M. – 8:30 P.M. • SALON E

Noise Correlations, Information, and Learning

Chair: Daniel Scott

Presenters: Daniel Scott, Chengcheng Huang, Jean-Paul Noel

Trial-to-trial variance is salient in neural activity. Even when stimulus properties are fixed, responsive neurons often produce different activity between one stimulus presentation and the next. These tuning-curve deviations are often correlated between neurons (and hence termed "noise correlations"), which means they cannot always be averaged away to recover full stimulus information. This panel addresses some of the many functional and theoretical impacts of noise correlations.

Daniel Scott will provide a brief review of work on noise correlations to date. He will then present work showing how noise correlations interact with three-factor Hebbian rules to control credit assignment during reinforcement learning.

Chengcheng Huang will show how circuit wiring and modulatory inputs impact information flow in spiking networks. She will show how network dynamic regimes determine noise correlations and information transfer, and will compare modeled activity to recordings from visual cortex during an attention task. This will address how attention may work to improve information flow by suppressing local cortical dynamics.

Jean-Paul Noel will show how lateral connectivity (putatively driving noise correlations) changes when tasks require usage of internal models rather than sensory evidence. When macaques are made to rely on internal models to navigate within a virtual environment, the pattern of lateral connectivity remained fixed in MSTd, while parietal and frontal cortices dynamically remap.

PANEL • MONDAY • 7:00 P.M. – 8:30 P.M. • ZIEGLER

An Introduction to Computational Psychiatry From Different Methodological Approaches

Chair: Isabel Berwian

Presenters: Frederike Petzschner, Oliver Robinson, Peter Hitchcock, Isabel Berwian

The panel will give an introduction to the research field "Computational Psychiatry". Each panelist will provide a didactic example and its application to show how generative models make precise predictions, which can be very useful to uncover disease mechanisms in psychiatry and develop tools for improving treatment response prediction. Frederike Petzschner will start with an introduction to model development and illustrate this approach by means of computational models of addiction and OCD and their application to a longitudinal study in patients with gambling disorder and patients with OCD. Next, Oliver Robinson will present a new simulation-based approach that allows to conduct meta-analyses across different tasks and models and applies this approach to show that "negative affective bias" in patients with mood and anxiety disorders across 27 studies are due to elevated punishment learning rates but not differences in punishment sensitivity.

Peter Hitchcock will argue for the untapped potential of using computational psychiatry methods to infer clinical principles to serve as a foundation for the next generation of psychotherapy. He will present an ongoing study in this vein that aims to uncover the principles of cognitive action learning and selection (such as learning to think abstractly versus concretely), with relevance to myriad psychotherapies. Finally, Isabel Berwian will present one specific computational tool that allows to disentangle anticipation and experience of effort and reward, its application to predict relapse after antidepressant discontinuation in a longitudinal patient study and how it can be used to uncover and dissociate predictors and mediators of response to Behavioral Activation therapy.

TUESDAY, FEBRUARY 1, 2022
TUESDAY MORNING PANEL SESSIONS

PANEL • TUESDAY • 7:30 A.M. – 9:30 A.M. • INDEPENDENCE AUDITORIUM

A Slippery Slope and Converging Circuit Trails for Chronic Pain and Addiction

Chair: Catherine Cahill

Presenters: Matthew Hearing, Claire Manning, Steven Nieto, Monique Smith, Catherine Cahill

There is extensive overlap between pain and reward circuits including mesocorticolimbic circuitry that received nociceptive input via spinal projections to various brain structures. This panel will update the recent pre-clinical mechanistic studies that provide evidence for neuroplasticity in these circuits that contribute to alter emotional states and facilitate the genesis of chronic pain and drug dependence. Dr. Matthew Hearing (Marquette Univ) will present published and unpublished data on sex-specific and exposure-dependent effects of remifentanil self-administration on prefrontal-accumbens and dorsal-striatal plasticity and how it relates to deficits in decision-making and habit-like drug taking. Dr. Claire Manning (Stanford) will present unpublished data effects of inflammatory pain on the synaptic function of an excitatory PAG-VTA circuit. She data suggests that 24 h following pain onset there no synaptic changes at PAG synapses onto VTA Dopamine neurons. Rather, that a postsynaptic alteration occurs at the PAG- VTA GABA neurons. Dr. Steven Nieto (UCLA) will present recent research on pain catastrophizing and its effects on alcohol cue-elicited neural activity among individuals with alcohol use disorder (AUD), where pain catastrophizing predicts greater cue-induced neural activation in the dorsal but not ventral striatum. Dr. Monique Smith established that mice exhibit empathy by rapidly adopting the sensory-affective state of a partner, regardless of the valence of the information. The social transfer of pain-related information (pain and morphine analgesia) was dependent upon ACC input activity to the NAc, whereas the social transfer of fear was dependent upon ACC- basolateral amygdala activity. These results suggest that the ACC generates a specific and appropriate empathic behavioral response by accessing distinct downstream targets in the striatum and amygdala. The mesolimbic dopamine system drives approach or avoidance behavior following a salient acute pain stimulus, but deficits in dopamine signaling emerge that impair motivated behavior in chronic pain states. Mu opioid receptors are present on both direct and indirect striatal circuits, but their role in

modulating pain and opioid analgesia remains unknown. Dr. Cathy Cahill will present unpublished data showing that conditional knockout of mu receptors from either dopamine D1 or D2 receptors did not affect sensory or affective dimensions of pain, however selective ablation produced opposing effects on opioid mediated analgesia and reward in models of tonic inflammatory and chronic pain. This data suggests that opioid modulation of medium spiny neurons can elicit divergent effects on opioid antinociception and negative reinforcement.

PANEL • TUESDAY • 7:30 A.M. – 9:30 A.M. • SALON B

Midbrain-Extended Amygdala Dysregulation in Stress and Addiction

Chair: Elizabeth Avegno

Presenters: Meghan Gallo, Dipanwita Pati, Elizabeth Avegno, Julie Fudge

Midbrain and extended amygdala subregions are interconnected via reciprocal circuitry, and individual midbrain-extended amygdala circuits are implicated in various facets of positive and negative reinforcement. This panel will highlight the complexity of this system by focusing on individual circuits between midbrain (here including ventral tegmental area [VTA] and periaqueductal gray [PAG]) and extended amygdala (here including central amygdala [CeA], bed nucleus of the stria terminalis [BNST], and the shell of the nucleus accumbens) subregions across species (mouse, rat, and non-human primate). Dysregulation of these circuits can arise as a consequence of stress or drug exposure, a concept that will be explored by each panelist.

Meghan Gallo (graduate student in the labs of Dr. Kevin Bath at Columbia University, and Drs. Michael Frank and Chris Moore at Brown University) will discuss dopamine signaling in the ventral striatum and disruptions in reward learning and decision making in mice after exposure to early life adversity. Dr. Dipa Pati (Postdoctoral fellow in Dr. Thomas Kash's lab, University of North Carolina) will then discuss PAG projections to the BNST and their contribution to pain-like behavior and dysregulation after chronic alcohol exposure in male and female mice. Dr. Elizabeth Avegno (Instructor, Louisiana State University Health Sciences Center) will discuss VTA projections to the CeA in mice and rats and explore alterations in this circuitry after chronic alcohol exposure, as well as the potential role VTA-CeA circuitry plays in anxiety-like behavior. Finally, Dr. Julie Fudge (Professor, University of Rochester) will then characterize BNST- and CeA-VTA circuitry in the non-human primate, and detail spatial and neurochemical characteristics of extended amygdala inputs into the VTA, with consideration to circuit implications in stress response.

PANEL • TUESDAY • 7:30 A.M. – 9:30 A.M. • SALON C

The Role of the Endocannabinoid Signaling in Both the Development and Maintenance of Substance Use Disorders

Chairs: Natalie Zlebnik, Jennifer Wenzel

Presenters: Anissa Bara, Jennifer Wenzel, Sam Bacharach, Jayme McReynolds

Substance use disorder (SUD) is a major public health concern with few available pharmacotherapies. A significant impediment to the development of pharmacological treatments for SUD is the extremely complicated nature of the disease, which is comprised of several different behaviors and associated underlying neurobiological mechanisms. Recently there has been an increased interest in targeting the endocannabinoid (eCB) system to treat SUD, stemming from its enrichment in brain regions known to play a role in SUD, and its involvement in a number of addiction-related behaviors. This panel will highlight new research on the role of the eCB system in various aspects of SUD, including: reward and reinforcement, incentive salience, stress-induced drug seeking, and the long-term risk of relapse following recovery. Anissa Bara will discuss how the study of the placenta (in humans and rodents) can help to identify early indices of psychiatric vulnerability and their developmental trajectory into adulthood after prenatal cannabis exposure. Jennifer Wenzel will discuss how exposure to exogenous cannabinoids in adolescence results in lasting deficits in dopamine system function and altered cocaine reward, self-administration, and cocaine-mediated anxiety in adult mice and rats. Sam Bacharach will discuss how individual differences in cue-motivated behaviors are regulated by both eCB signaling in the ventral tegmental area and dopamine transmission in the nucleus accumbens using a Pavlovian lever autoshaping task in rats. Jayme McReynolds will present findings from behavioral and electrophysiological studies showing how acute and chronic stress recruits eCB machinery to promote cocaine-taking and seeking behavior in rats. Altogether, these talks will provide an overview of our current knowledge on the myriad roles that the eCB system plays in addiction-related behaviors and highlight relevant neurocircuitry that may provide new avenues for therapeutic investigation.

PANEL • TUESDAY • 7:30 A.M. – 9:30 A.M. • SALON D

Structure, Trafficking, and Function of Glutamate Receptors

Chair: Johannes Hell

Presenters: *Terunaga Nakagawa, Andres Maricq, Roger Nicoll, Françoise Coussen-Choquet*

Most synapses in the brain are glutamatergic. AMPARs mediate most of basal synaptic transmission and their dysfunction underlies many brain disorders. Hell will chair this panel and introduce the general topic. Different aspects of the structure, trafficking, regulation, and function of AMPARs will be discussed. Nakagawa will present new cryo-EM structures of the AMPAR in complex with the auxiliary subunit stargazin and discuss implications in the mechanism of gating modulation by stargazin. Maricq will describe

molecular machinery required for kinesin-mediated delivery of AMPARs to synapses. Two convergent signaling pathways (CaMKII and MAPK) coordinate the loading of synaptic AMPARs onto JIP-family scaffold proteins, and scaffold proteins onto kinesin motors, thus providing a mechanism for experience-dependent changes in synaptic strength. Nicoll will show physiological data that address how well properties of the Ca- and Calmodulin – dependent kinase CaMKII can account for long-term potentiation. This talk will explore the role of different properties of CaMKII such as the potential exchanged of naïve unphosphorylated subunits of this dodecameric kinase to perpetuate memory. Françoise Coussen will talk about the role of intracellular transport of AMPA receptor in basal condition or after LTP in cultured hippocampal neurons or in organotypic slices. She will show how specific cytosolic partners of GluA1 can modulate the transport of AMPA receptor in basal conditions and after LTP. This presentation will provide new insight of the role of neosynthetized AMPA receptor for the synaptic physiology.

PANEL • TUESDAY • 7:30 A.M. – 9:30 A.M. • SALON E

Path From Short-Term to Chronic mTBI is Paved With Astroglial Tiles---New Insights Into the Evolution of Blast-Related Astrocyte Dysfunction and Pathology

Chair: Daniel Perl

Presenters: David Priemer, David Cook, Annalisa Scimemi, Greg Elder

Dr. Perl will introduce and moderate the panel. Blast exposure, a common cause of TBI in modern warfare, often evolves to a persistent postconcussion syndrome (PCS) associated with cognitive issues, sleep dysfunction and post-traumatic stress disorder (PTSD). Recent human neuropathology evidence and animal models suggest that damage to astrocytes may play an important role in the pathophysiology underlying PCS. This panel will explore evidence supporting this concept.

Dr. Priemer will demonstrate prominent morphologic changes in neocortical astrocytes of Service Members who experienced multiple blast exposures. The dystrophic astrocytes are found in a unique distribution pattern that reflects blast biophysics, strongly suggesting they have been damaged by the blast wave.

Using state-of-the art confocal/super-resolution microscopy, Dr. Cook will describe marked disturbances in astrocyte architecture following blast TBI. The normal 'tiled' pattern of uniform EAAT2 expression in finely ramifying astrocyte processes that envelope synapses is markedly disrupted in human specimens. EAAT2 is responsible for clearing synaptically-released glutamate in these brain regions. Such dysmorphology impairs synaptic network function, supporting the idea that these pathologic features of astrocytes disturb brain function.

Dr. Scimemi will show how astrocyte remodeling modifies synaptic transmission in mouse hippocampus at different times in the circadian cycle, interfering with the execution of certain hippocampal-dependent behaviors. These findings highlight important mechanisms by which neurons and astrocytes modify the molecular composition and structure of the synaptic environment. Along with the findings in the two preceding talks, these data raise the possibility that blast-related astrocytic dysmorphology could also influence neural circuits affecting sleep cycles.

Dr. Elder will explain how astrocyte-neurovascular interactions in blast-exposed rats are disrupted. As these pathogenic processes evolve over months, aberrant increases in the metabotropic glutamate receptor (mGluR2) which initially develop in neurovascular compartments, then spread to the CNS synaptic parenchyma of multiple brain regions, marking the emergence of PTSD-like behavioral traits in blasted rats.

PANEL • TUESDAY • 7:30 A.M. – 9:30 A.M. • ZIEGLER

To Reward Prediction Errors..... and Beyond!

Chair: Melissa Sharpe

Presenters: Erin Calipari, Melissa Sharpe, Paul Phillips, Kauê Costa, Kate Wassum

Dopamine neuron firing and release consistently correlates with the unitary, scalar-value error found in temporal difference reinforcement learning (TDRL) algorithms. However, evidence continues to emerge that pushes at the limits and constraints that circumscribe the TDRL error signal in classic models. This panel will review some such evidence, focusing on studies being done by five labs - in rats and mice, using techniques as diverse as computational modeling, voltammetry, photometry, unit recording, and optogenetics - that collectively challenge the TDRL framework. This will begin with Erin Calipari (Vanderbilt University), who will present evidence that dopamine transients play a causal role in latent inhibition, which is inconsistent with error-based accounts and instead more related to salience. Melissa Sharpe (UCLA) will present data that tests how in-vivo stimulation of midbrain dopamine neurons is encoded from a cognitive perspective in the brain, finding data that is inconsistent with this manipulation being generally rewarding, as would be predicted by TDRL accounts. Paul Phillips (University of Washington) will describe how mesolimbic dopamine encoding of task parameters is affected during the transition from flexible to inflexible behavioral control. Kauê Costa (NIDA) will provide evidence from optophysiological recordings showing that dopamine release in the ventral striatum reflects value-less prediction errors that correlate with sensory-sensory learning. Finally, Kate Wassum (UCLA) will present evidence showing that dopamine transients are used in amygdalar circuits to update sensory-specific reward associations. Together these findings are consistent with an emerging consensus that the dominant account does not fully capture the scope of dopamine's role in shaping our ability to learn about – and respond to - the world around us.

PANEL • TUESDAY • 4:30 P.M. – 6:30 P.M. • INDEPENDENCE AUDITORIUM

Data-driven Approaches to Enhancing Diversity, Equity, and Inclusion in STEM

Chair: Michael Stefanik

Presenters: Veronica Martinez-Acosta, Kyle Frantz, Sade Spencer, Michael Taffe

Diversity, equity, and inclusion (DEI) initiatives in STEM seek to provide tools expanding access to STEM education, strengthen diversity in the workforce, and amplify underrepresented and marginalized voices. The panel will provide perspectives on key challenges across DEI efforts in STEM and speak to the use of data to reveal and combat inequities in the career development timeline.

Veronica Martinez-Acosta (University of the Incarnate Word) will discuss hands-on approaches to teaching that support students with varying degrees of STEM experience by providing authentic data collection experiences. Encouraging creativity and allowing students to 'play with data' (while collecting, representing, and interpreting it), demonstrates significant benefits to students in preparation for graduate education and the STEM workforce. Kyle Frantz (Georgia State University) will show a minority-majority student population holds great potential to help diversify the professional workforce. Using a university-level center, DEI work inspires students from all backgrounds to see themselves in pathways toward professional careers, then supports concrete steps required to get there. A system of predictive analytics combined with faculty nominations also helps recruit students by suggesting a student could excel in advanced degree programs. Sade Spencer (University of Minnesota) will address persistent gender inequities in the distribution of salary, resources, and leadership opportunities for faculty in STEM. She will further discuss institutional policies and programs to address these issues and promote gender equity, diversity, and inclusion. Michael Taffe (UC San Diego) will discuss the implications of a funding disparity identified by the NIH which disadvantages Black applicants relative to white Principal Investigators. In addition, he will address how a related disparity of grant funding based on the research topics proposed leads to a disparity in funding for research that addresses the health concerns of communities of color.

PANEL • TUESDAY • 4:30 P.M. – 6:30 P.M. • SALON B

The Role of Microcircuits in the Striatum

Chairs: Suzanne Nolan, Lillian Brady

Presenters: Veronica Alvarez, Lillian Brady, Suzanne Nolan, Jordan Yorgason

Local microcircuit regulation of dopamine release is a fundamental process mediated by a variety of mechanisms, all acting in concert to regulate the timing and magnitude of signaling events - independent of action potentials. While much is known, emerging data show that there is a wealth of processes still yet to be probed within the striatum. First, Dr.

Veronica Alvarez will present recently published data showing that dopamine modulates the excitability of striatal projection neurons via modulation of the local inhibitory transmission among neurons. The findings reveal synapse-specific modulation by dopamine which involves the canonical GPCR known to bind dopamine as well as a significant contribution by 5HT receptors. Dr. Lillian Brady will next provide data characterizing the neural circuits and mechanisms that underlie reward learning and information encoding in both male and female subjects. Specifically, the presentation will demonstrate sex-specific cholinergic regulation of dopamine release mechanisms through nicotinic acetylcholine receptors expressed on dopamine terminals in the nucleus accumbens core that mediate sexually dimorphic behavior. Next, Dr. Suzanne Nolan will provide data revealing compartment-specificity in mechanisms of dopamine release regulation and experience-dependent plasticity across the terminal and somatodendritic compartments of the mesolimbic dopamine population, highlighting these processes as an important substrate of reward learning. Dr. Jordan Yorgason will close our symposium by presenting on cholinergic regulation of dopamine release, including findings on spontaneously occurring dopamine transients that differ in release and clearance across striatal subregions in a sex-dependent manner, and the effects of alcohol on transients in the NAc core andthe involvement of alpha-6 subunit containing nicotinic acetylcholine receptors. Together, these data will highlight the diversity and complexity of roles that striatal microcircuitry play in dopaminergic regulation. Understanding the intricacies of local regulation of dopamine signaling allows the construction of comprehensive frameworks of how activity within the dopamine system is integrated to drive downstream signaling and influence behavior.

PANEL • TUESDAY • 4:30 P.M. – 6:30 P.M. • SALON C

How Maternal Stress Shapes Offspring Brain Development and Behavior: Integrating Behavioral, Neurobiological, and Molecular Data From Clinical and Preclinical Studies

Chair: Christoph Anacker

Presenters: Milenna van Dijk, Rodrigo Grassi-Oliveira, Christoph Anacker, Annamaria Cattaneo

Stress is a major risk factor for mental illness, but there is a significant knowledge gap on how stress that is experienced in one generation may also affect the next generation. A mother's stress experience can cause psychopathology in her kids, but the biological mechanisms by which maternal stress impacts offspring brain function and behavior are largely unknown. This symposium will integrate epidemiological, genetic, neurobiological, and molecular findings from human and rodent studies to identify potential pathways and interventions for maternal stress effect transmission to the offspring. Dr. Milenna van Dijk will present epidemiological and neuroimaging data from a three-generation clinical study, showing that early life trauma interacts with cumulative genetic risk for depression to predict smaller hippocampal dentate gyrus (DG) volume. She will also show that a mother's parenting stress mediates associations between maternal depression and offspring depressive outcomes, cognitive impairments, and decreased DG structure. Dr. Rodrigo Grassi-Oliveira will present neurobiological data from complementary rodent models, showing that corticotrophin releasing factor (CRF)

signaling in the bed nucleus of the stria terminalis (BNST) of lactating mice decreases maternal care, resulting in robust differences in offspring behavior in adulthood. To better understand biological mechanisms and potential points of interventions in offspring, Dr. Christoph Anacker will discuss data from transgenic mouse models showing that the serotonin system determines offspring vulnerability to maternal stress by regulating DG neural activity and inflammation. Lastly, Dr. Annamaria Cattaneo will highlight the impact of stress during pregnancy, by integrating data from rodent prenatal stress models and clinical cohorts. She will discuss the role of inflammation and epigenetic signaling in the transmission of prenatal stress effects to the offspring. The state-of-the-art translational neuroscience highlighted in this symposium will integrate several layers of analysis in mothers and offspring across clinical and preclinical studies, with the goal to advance our understanding of potential points of intervention to interrupt the cycle of intergenerational stress transmission and psychopathology.

PANEL • TUESDAY • 4:30 P.M. – 6:30 P.M. • SALON D

Insular Cortex: The Island of Mis-Regulated Motivational and Affective States

Chair: Samuel Centanni

Presenters: Woody Hopf, Sarah Stern, Samuel Centanni, Melanie Pina

Dysfunctional emotional regulation is highly comorbid with many neuropsychiatric disorders including, but not limited to, affective, substance use, and eating disorders. The insula is an expansive brain area spanning the anterior-posterior gradient in the brain, and specific insular subregions seem to uniquely contribute to emotional and motivational behavioral output through intricate circuitry with cortical and subcortical brain regions. However, the precise circuitry and molecular mechanisms governing the insula's involvement in these behaviors has not been fully elucidated. This panel will present exciting new data exploring different insula-centric circuitry in the context of substance use disorder, stress, and food overconsumption. First, Woody Hopf (Indiana University) will present work on how anterior insula neurons encode drive for alcohol with and without aversive consequences, and how different insula populations may promote different aspects of alcohol pathology. Sarah Stern (Max Planck Florida) will then speak about the identification of nitric-oxide synthase-1 neurons in the mid-insula that project to the central amygdala and promote overconsumption in response to learned cues. Next, Sam Centanni (Vanderbilt), will discuss recent work examining a unique motor cortex-to-mid-insula-to-BNST circuit that is involved in monitoring active escape behavior during an inescapable stressor and subsequent negative affect behavior. Lastly, Melanie Pina (UNC Chapel Hill) will present work exploring how dynorphin and kappa opioid receptor microcircuit elements in the mid-insula support escalated alcohol-drinking behavior. Together, this session will detail essential novel research focused on an exciting brain region emerging as an integral regulator of behavioral output. Interventional strategies aimed at mitigating dysfunctional insula circuitry can have broad implications for curbing affective and motivational states driving many neuropsychiatric disorders.

PANEL • TUESDAY • 4:30 P.M. – 6:30 P.M. • SALON E

Neural Circuit Mechanisms of Psychedelic Action

Chairs: Yi Zuo, Christopher Niell

Presenters: Alex Kwan, Ju Lu, Cristopher Niell

Psychedelic drugs exert powerful and fascinating effects on the human mind. After a thirty-year hiatus due to regulatory restrictions, research interest in their mechanisms of action and therapeutic potentials has revived. Human clinical studies suggest that they may be efficacious in treating a variety of mental health problems ranging from alcoholism to depression and anxiety; however, the underlying neural processes are poorly understood. Rodent models provide an opportunity to investigate the molecular, cellular, and neural circuit mechanisms of the effect of psychedelic drugs. In this panel, Dr. Yi Zuo (University of California Santa Cruz) will give an overview of recent work on psychedelics and their impact on rodent brain circuits and behavior. Dr. Alex Kwan (Yale University) will talk about effects of psilocybin on the morphology and function of frontal cortical pyramidal neurons. Dr. Cristopher Niell (University of Oregon) and (University of Oregon) will discuss how serotonergic-2A activation affects visual sensory responses and large-scale neural activity. Dr. Ju Lu (University of California Santa Cruz) will discuss how a novel non-hallucinogenic psychedelic analog rescues the deleterious effects of stress at the synaptic, circuit, and behavioral levels in mice. The panel will conclude with discussion and questions.

PANEL • TUESDAY • 4:30 P.M. – 6:30 P.M. • ZEIGLER

Distributed Orbitofrontal Cortex Circuits Coordinate Adaptive Decision Making

Chair: Dan Li

Presenters: Dan Li, Christina Gremel, Stephanie Groman, Tony Ye

The orbitofrontal cortex (OFC) supports adaptive, outcome-guided decision making across a diverse array of behavioral tasks. However, the extended neural circuitry and cellular mechanisms by which specific decision variables are conveyed to, converge within, and are accessed by OFC networks are still being defined. Our panel will address the following topics: 1) Mr. Li (from the Gourley lab) will define an integrated amygdalo-fronto-striatal network coordinating discrete features of flexible learning and memory – the encoding, stable representation, and retrieval of decision variables across time and OFC-connected brain regions. 2) While OFC and its outputs have been implicated in certain goal-directed behaviors, including the processing of outcome-related information, less clear is whether this includes inferred action-contingency-related information. By imaging and manipulating the OFC in a cell-type and projection-specific manner, Dr. Gremel will examine whether the OFC shows and uses recent action-contingency information to support goal-directed control of behavior. 3) Next, Dr. Groman will describe how individual OFC circuits encode discrete reinforcement-learning processes that guide choice behavior in rats. She will present new evidence indicating that cortico-cortical circuits play a critical role in maintaining value representations and describe how multiple

OFC circuits may interact in normal and abnormal states to influence decision making. 4) Finally, Dr. Ye (from the Izquierdo lab) will discuss how theta (5-10 Hz) oscillations in anterior cingulate and OFC are involved in flexible stimulus- and action-based learning using a combination of simultaneous in vivo electrophysiology and inhibitory chemogenetic manipulations. Throughout, Dr. Gourley will lead the discussion by integrating these findings with an emphasis on translational implications and emerging hypotheses.

BRAIN TALK TOWN HALL MEETING

BRAIN TALK • TUESDAY • 7:00 P.M. – 8:30 P.M. • SALON B

Considering Psychedelic Therapies in Mental Health

Presenter: Rachel Yehuda

Can psychedelics be used safely and effectively in psychotherapy? Until recently, the fields of neuroscience and psychiatry portrayed psychedelic drugs as dangerous neurotoxins, and the FDA maintains MDMA as a Schedule 1 drug – a drug with no medical benefit and the potential for harm. Although new findings present a far more encouraging view of MDMA's effects on the brain, there continues to be suspicion concerning its safety and therapeutic potential. But the tide is turning. This presentation will provide a brief history of how MDMA has been portrayed in the last 40 years and will provide updated knowledge about how MDMA works in the brain. There is a major shift occurring in the way that psychedelics are viewed. Even individuals in the most conservative corners of mainstream science and mental health are recognizing that the effects MDMA when used as a party drug without protocols for preparation, intention, and clinical supervision, are very different from MDMA-assisted psychotherapy, in which professionals trained to work with clients in altered states offer a structured, safe, and healing experience, followed by the opportunity to process the new insights gained from the therapy. The promising results from Phase 2 and Phase 3 clinical trials of MDMA-assisted psychotherapy in post-traumatic stress disorder (PTSD) have given rise to a new optimism for the treatment of challenging mental health conditions.

WEDNESDAY, FEBRUARY 2, 2022

WEDNESDAY MORNING PANEL SESSIONS

PANEL • WEDNESDAY • 7:30 A.M. – 9:30 A.M. • INDEPENDENCE AUDITORIUM

Epigenomic Approaches to Decoding Neural Circuits and Psychiatric Disorders

Chair: Anne West

Presenters: Anne West, Marija Kundakovic, Elizabeth Heller, Hyejung Won

This panel feature four young innovators in neuroepigenomics who are discovering how chromatin regulation coordinates neural function in the normal brain and in neuropsychiatric disorders. Dr. West will discuss her studies aimed at addressing how

mutations in chromatin regulators disrupt synapse development in autism and intellectual disability. Her lab is using maturation of cerebellar granule neurons in the mouse as a model system for linking developmental plasticity of the epigenome with circuit formation and function. Dr. Kundakovic will show that 3D chromatin organization in the mouse brain differs between males and females and undergoes dynamic remodeling during the female ovarian cycle. This cyclical, sex hormone-driven dynamism in 3D genome organization is enriched for brain disorder-relevant genes and pathways, providing a novel molecular framework to understand female-specific gene regulation, neuroplasticity, and disease risk. Dr. Heller will present data on bivalent chromatin profiles, which contain both active and repressive chromatin modifications. She will show how these profiles change in mouse striatum following cocaine abstinence to effect long-lasting changes in gene expression, and she will showcase novel methods of neuronal-subtype-specific chromatin profiling and locus specific epigenetic editing using CRISPR. Finally, Dr. Won will show how chromosome conformation facilitates large-scale annotation of non-coding variants. She will introduce a novel platform her lab developed that annotates non-coding variants based on chromosome conformation in the human brain. She will also discuss about how chromosome conformation differs between neurons and glia, which highlights the importance of building cell-type specific gene regulatory relationships in understanding disease mechanisms underlying psychiatric disorders.

PANEL • WEDNESDAY • 7:30 A.M. – 9:30 A.M. • SALON B

Sticking a Spork in Opioid Reward, Motivation, and Pain: A Neural Circuit and Sex-Specific View of Factors Influencing Opioid Use and Abuse

Chair: Suman Guha

Presenters: Bailey Sarka, Devan Gomez, Suman Guha

Although pandemic-related public health has come to dominate headlines, the opioid epidemic continues to silently rage in the US. In the first year of the pandemic alone, opioid-related overdose deaths have risen 36.4% to 69,006 in 2020 highlighting the severity of opioid abuse. In this symposium, we will provide recent findings on the mechanisms and neural circuitry underlying opioid-mediated analgesia, motivation to seek opioids, and novel therapeutic approaches to opioid abuse. We will address sex-specific effects at all levels of analysis. Bailey Sarka will show how neuropathic pain impacts oxycodone seeking behavior and electrophysiological properties of drug-seeking medial prefrontal neuron ensembles vs non-ensemble neurons. Additionally, she will cover sex differences in both seeking behavior and electrophysiology. Devan Gomez will discuss sex-specific effects protracted morphine withdrawal has on morphine self-administration and shifts from food- to morphine-related motivated behavior. Sex-specific electrophysiological data will also be presented that correlate these behavioral changes to adaptations within mesoaccumbal subcircuit-specific dopamine cells, complimented by DREADD manipulations aimed at identifying causation of these shifts in behavior. Suman Guha will discuss the relationship between severity of addiction-like behavior and anhedonia-like states in rats — as measured using intracranial self-stimulation (ICSS). The focus of his talk will be on how anhedonia-like state is associated with progression to

compulsive-like opioid self-administration, cue- and context-induced relapse, and how these vary in female and male subjects. Understanding the mechanisms underlying the analgesic, motivational, and rewarding effects of opioids will promote the development of better treatments for reduction of opioid abuse and overdose death.

PANEL • WEDNESDAY • 7:30 A.M. – 9:30 A.M. • SALON C

Innovative Pharmacotherapeutic Strategies for Treating Psychiatric Disease from Bench to Bedside

Chair: Sade Spencer

Presenters: Sade Spencer, Kolter Grigsby, Lara Ray

In recent years, many large pharmaceutical companies have divested their interest in neuropsychiatric drug development. One reason for this pivot may be the perceived and actual translation gap between bench and bedside. The increasing recognition of these difficulties by pharmaceutical companies and researchers alike has inspired contemporary neuroscientists to explore innovative ways to close that gap. An iterative process of forward and reverse translation is important for the future of neuropsychiatric drug development and successful implementation of new clinical treatments. This panel brings together preclinical and clinical researchers investigating innovative pharmacotherapeutic strategies for treating neurological and psychiatric diseases. Sade Spencer (University of Minnesota) will present preclinical research related to repurposing the diabetes drug metformin as a novel therapy for cocaine relapse. Kolter Grigsby (Oregon Health and Science University) will present a set of collaborative findings highlighting that the phosphodiesterase type-4 inhibitor, apremilast, suppresses excessive alcohol drinking across the spectrum of alcohol use disorder (AUD) severity. Speaking directly to the aforementioned “translation gap,” Lara Ray (University of California Los Angeles) will discuss a rational model for determining whether signal in behavioral pharmacology outcomes in the human laboratory predicts the efficacy of a medication in a clinical trial.

PANEL • WEDNESDAY • 7:30 A.M. – 9:30 A.M. • SALON D

The Role of Chromatin Remodeling in Mental Health and Disease

Chairs: Philipp Mews, Iva Zovkic

Presenters: Iva Zovkic, Philipp Mews, Alberto Lopez, Marcelo Wood

We are still at the frontier of understanding how and to what extent epigenetic regulation governs brain function in mental health and disease. This panel will present emerging data that converge on the notion that chromatin remodeling drives learning-induced gene activity and reinforces long-last behavioral changes in neuropsychiatric disorders. Recent work by Iva Zovkic (U Toronto) established histone variants as novel regulators of memory, whereby enrichment of H2A.Z, a variant of histone H2A, impairs memory formation. She will present new insights into the distinct roles of macroH2A histone variants in learning-induced gene expression and memory formation. Philipp Mews (Icahn School of Medicine at Mount Sinai) will discuss the significance of circuit-specific

chromatin remodeling in the nucleus accumbens for substance use disorder, and how histone variant exchange supports long-lasting changes in drug-related gene regulation, circuit connectivity, and behavior. Alberto Lopez (Vanderbilt University) will share new data that link cocaine-induced histone acetylation by KAT2A to long-lasting changes in gene regulation and circuit function that make animals vulnerable to relapse. Marcelo Wood (UC Irvine) will present how subtype-specific control of striatal histone acetylation by HDAC3 regulates cocaine-associated behaviors. Together, this session will showcase how innovative epigenetic technology in animal models has helped advance studies of reward processing. Developing a mechanistic understanding of how circuit activity and neuro-epigenetic remodeling cooperate to shape behavior will ultimately pave the way towards novel therapeutics for neuropsychiatric disorders.

PANEL • WEDNESDAY • 7:30 A.M. – 9:30 A.M. • SALON E

Neural Circuits for Visual Information Processing and Behavior

Chair: Huizhong Tao

Presenters: Aaron McGee, Sandra Kuhlman, Jason Samonds, Cristopher Niell

Neural circuits in the mammalian visual system perform 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 environmental contexts and statistics of visual scenes. 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 now being addressed with enriched imaging, electrophysiology, optogenetics and behavioral approaches in head-fixed and freely moving animal preparations. In this panel, Dr. Aaron McGee (ULouisville) will present recent calcium imaging results on how monocular deprivation during the critical period disrupts binocularity, orientation, and spatial frequency tuning by tracking thousands of neurons in the mouse visual cortex. Dr. Sandra Kuhlman (CMU) will discuss recent findings demonstrating maturation of neuronal responses to complex natural scene stimuli over a protracted post-eye-opening period and its sensitivity to the disruption of visual input. Dr. Jason Samonds (UTA) will discuss recent results on binocular eye alignment, disparity responses, and depth discrimination in both controlled and natural conditions to provide new understanding of how binocular vision is used to stereoscopically derive information about depth. Dr. Cris Niell (UOregon) will describe measurements of visual responses in large populations of visual cortical neurons in freely moving mice and how they encode a combination of visual and self-movement signals in a cell-type dependent manner. And Dr. Huizhong Tao (USC) will discuss recent findings on the contributions of distinct collicular circuits to visual looming stimuli induced defensive behaviors. Together, these presentations will provide diversified views on circuit mechanisms underlying visual perceptual functions and behaviors.

PANEL • WEDNESDAY • 7:30 A.M. – 9:30 A.M. • WANDERLUST

Cell Type and Circuit Specific Changes Contributing to Neurodevelopmental and Psychiatric Disorders

Chair: Amelia Gallitano

Presenters: Amelia Gallitano, Robert McCullumsmith, Consuelo Walss-Bass

This panel will feature distinct approaches to assess cell-subtype specific gene expression and function relevant for disorders ranging from the neurodevelopmental disorder dyslexia to neuropsychiatric disorders including schizophrenia and opioid use. Dr. Gallitano (University of Arizona) will describe findings from single cell RNAseq studies investigating how sleep deprivation alters gene expression in neurons and microglia of the mouse frontal cortex, and how the immediate early gene transcription factor Egr3 influences cell type specific gene expression in response to this environmental stimulus. Dr. Mccullumsmith (University of Toledo) will present data on gene expression differences identified in cortical layer specific pyramidal neurons between schizophrenia patients and controls identified from postmortem laser capture microdissection, identifying several novel pathways, including ubiquitin-independent protein catabolic process. Dr. Walss-Bass (University of Texas) will present findings of cell-type specific effects of opioid exposure in human postmortem brain and iPSC-derived neurons. Taken together, these findings highlight the importance of studying CNS disorders at the cellular level, revealing novel insights for the pathophysiology of these often-disabling conditions.

PANEL • WEDNESDAY • 7:30 A.M. – 9:30 A.M. • ZIEGLER

Signaling, Composition and Modulation of Synaptic AMPA Glutamate Receptors

Chair: Johannes Hell

Presenters: Maria Kurnikova, Daniel Choquet, Olivia Buonarati, Johannes Hell

AMPA receptors (AMPARs) mediate the majority of signal transmission at excitatory synapses, they are central to synaptic plasticity mechanisms, and are emerging drug targets. NMDA receptors (NMDARs) are important for triggering synaptic plasticity. This panel will present recent advances in the understanding of the structure of AMPARs, their trafficking to postsynaptic sites, and the function of AMPARs and NMDARs in postsynaptic signaling. The talks will cover a wide range of experimental approaches, including structural analysis, electrophysiology, pharmacology, and super-resolution light microscopy. Maria Kurnikova (Carnegie Mellon University) will present computational molecular dynamics modeling of the AMPA receptor structural dynamics in the open and closed states. She uses machine learning (ML) to infer dynamic relationships between the ligand binding domain tetramer conformation and the structure of the ion channel gate. She will also present modeling of the AMPA receptor interaction with the non-competitive inhibitors GYKI, Perampanel and 4-BCCA. Daniel Choquet (University of Bordeaux) will discuss the role of AMPAR lateral diffusion in both short-term and long-term synaptic plasticity in situ and in vivo, and the central role of this process in various learning

paradigms. Olivia Buonarati (University of Colorado, Denver) will describe a non-ionotropic NMDAR function in a form of LTP that requires Ltype Ca2+ and CaMKII. Johannes Hell (UC Davis) will present data that indicate that intracellular signaling of norepinephrine stimulates trafficking of AMPARs to the surface and how this mechanism contributes to LTP induced by a combination of a 5 Hz prolonged tetanus and beta-adrenergic signaling that is induced by norepinephrine.

PIONEER SESSION #2

PIONEER SESSION • WEDNESDAY • 9:45 A.M. – 11:00 A.M. • ZIEGLER

Drugs and Peptides: One Woman's Journey Through the Brain

Pioneer: Jacqueline McGinty

Chair: Matthew Hearing

Investigators: Matthew Hearing, Jamie Peters

During my early years in research, I focused on the distribution and regulation of opioid peptides. With collaborators, I discovered that enkephalin is expressed in photoreceptors of the lobster eye, that opioid peptides are differentially expressed in the mediobasal hypothalamus as well as in cortical interneurons, and that their expression is upregulated by excitatory activity in hippocampal mossy fibers. Crossing the bridge to the striatum, we discovered that dopamine D1 and D2, as well as muscarinic, receptors differentially regulate enkephalin and dynorphin expression and phosphoprotein signaling in direct and indirect pathway neurons. Functionally, presynaptic kappa opioid receptor stimulation suppressed amphetamine-induced increases in extracellular levels of dopamine and glutamate in dorsal and ventral striatum. With colleagues in MUSC's Addiction Research Center, we expanded our focus to cocaine induction of immediate early genes and phosphoprotein signaling in prefrontal cortex. We discovered that infusion of BDNF into the prelimbic cortex immediately after the end of cocaine self administration prevented relapse to cocaine seeking by preventing dephosphorylation of plasticity-related proteins that underlie hypofrontality during early withdrawal. Further, we demonstrated that BDNF regulates prelimbic pathway-specific output, with opposing prelimbic input to the nucleus accumbens and paraventricular thalamic nucleus (PVT) underlying relapse to cocaine seeking. Finally, our most recent work implicates differential intrinsic excitability changes in prelimbic D1 and D2 receptor-expressing neurons that project to nucleus accumbens in heroin-seeking after abstinence. WCBR has played a large role in my journey through the brain over the years, as we mapped the regulation of reward-related circuits by addictive drugs with increasing resolution, a mantle picked up by Matt Hearing and Jamie Peters, the young investigators whom I have chosen to speak in this session.

PROFESSIONAL DEVELOPMENT SESSION #2

SPECIAL SESSION • WEDNESDAY • 2:00 P.M. – 3:30 P.M. • INDEPENDENCE AUDITORIUM

The Lifecycle of an NIH Grant Application: From Inspiration to Frustration to Celebration

Chair: Lakshmi Devi

Presenters: Bradley Cooke, Ryan Lalumiere, Laura O'Dell, Lakshmi Devi, Qingchun Tong, Matt Carter, David Barker

The career development forum is intended for students, postdocs and new investigators who are not yet familiar with the intricacies of grant applications to the National Institutes of Health. Attendees will learn about the types of grant applications suitable for different phases of one's career, initiatives to increase diversity in the scientific workforce, the different Institutes and Centers at the NIH that fund research, and how the NIH evaluates grant applications and makes funding decisions. Tips on grant writing will be provided, including timelines and planning, who to contact and when, the myriad forms and documents required, and what to expect in terms of feedback from the NIH. The talk will be followed by a mock study section, intended to convey the basic events that occur when an application is discussed in a study section at the Center for Scientific Review at NIH. The mock study section will introduce to attendees the Scientific Review Officer, the panel Chair, and reviewers, as well as provide a sense of what reviewers are looking for when they read and discuss a grant application. There will be time for questions for the panelists after the mock study section.

WEDNESDAY AFTERNOON PANEL SESSIONS

PANEL • WEDNESDAY • 4:30 P.M. – 6:30 P.M. • INDEPENDENCE AUDITORIUM

Prediction and Treatment of Risk Factors for Suicide

Chair: Anil Malhotra

Presenters: Anna Van Meter, Caitlin Millett, Colleen Hanlon, Miklos Argyelan

The relationship between mood and self-injurious behaviors such as heavy alcohol use with suicide risk represents a significant public health challenge. In this panel, we will explore novel approaches to assessing and treating these critical manifestations of psychopathology. Anna Van Meter (New York University) will begin with a discussion of suicide among youth. Novel methods of assessment, including digital phenotyping, ecological momentary assessment, and patterns in online activity, may overcome the limitation of self-reported suicidal thoughts or behaviors. Katherine Burdick (Harvard) will present on suicide in bipolar disorder (BD). 25-60% of BD patients will make at least one suicide attempt in their lives; 4-19% will succeed. In a cohort of 260 BD patients, 97 had made at least one prior attempt. Degree of current suicidal ideation (SI) correlated with levels of the anti-inflammatory cytokine Interleukin 1 receptor antagonist – the association was only seen in patients with a history of prior attempt (r=-0.29; p=0.01), not

in those without (r=-0.05; p=0.59). These data point to a possible biomarker of SI and may have therapeutic implications. Colleen Hanlon (Wake Forest) will present on a novel treatment approach to a major risk factor for suicide, excessive alcohol use. Rates of heavy drinking have escalated dramatically since 2019, particularly in middle-aged women and older adults. One of the primary factors driving accelerated drinking has been an increase in dysphoric mood and anxiety. She will present data demonstrating that non-invasive stimulation of the dorsal medial prefrontal cortex may improve mood and decrease daily alcohol consumption among individuals seeking to cut back their alcohol use. Finally, Miklos Argyelan (Hofstra) will present on electroconvulsive therapy (ECT) and suicide. He will show the neuroimaging effects of ECT in treatment resistant depression and will evaluate relationships between biomarkers of reward sensitivity and suicide.

PANEL • WEDNESDAY • 4:30 P.M. – 6:30 P.M. • SALON B

Dopaminergic Pathways in Adaptive and Maladaptive Behaviors

Chairs: Munir Kutlu, Jennifer Zachry

Presenters: Ted Hsu, Talia Lerner, Munir Kutlu, Jennifer Zachry

Dopamine and areas innervated by dopaminergic projections represent important substituents of adaptive behavior and disturbances in these pathways support maladaptive behaviors. This panel will overview current research on dopaminergic pathways in adaptive and maladaptive behaviors across striatal, cortical, and midbrain areas as it relates to goal-directed behavior, compulsive reward seeking, associative learning, and reinforcement learning. First, Dr. Ted Hsu will present work examining the novel hypothesis that first order thirst and hunger detectors utilize the lateral hypothalamic area as a relay region to communicate need state information to ventral tegmental area dopamine neurons in order to invigorate goal-direction. Next, Dr. Talia Lerner will present work on how dopamine, a critical modulator of striatal synaptic plasticity, controls alterations in corticostriatal circuits leading to the development of compulsions (defined as continued reward-seeking in the face of punishment) using dual-site fiber photometry to measure dopamine axon activity in the dorsomedial striatum and the dorsolateral striatum as compulsions emerged. Following, Dr. Munir Gunes Kutlu will present work on information encoding at the single cell level in the nucleus accumbens defining functional roles of individual cells via a neural network model in a fear conditioning task. Jennifer Zachry will follow this work with a presentation on the distinct but complementary contributions of Dopamine-1 and -2 medium spiny neurons in the accumbens core to associative learning. She will share foundational evidence for the discrete aspects of information that are encoded within these cellular populations as a follow up to Dr. Kutlu's work on the functional roles of all accumbal neurons. Overall, these talks will showcase new and exciting research on the role of the dopaminergic pathway in a range of behavioral outcomes and therefore, will be of interest to the diverse attendees of the WCBR.

PANEL • WEDNESDAY • 4:30 P.M. – 6:30 P.M. • SALON C

Cortical Mechanisms of Pain Modulation

Chair: Matthew Banghart

Presenters:Matthew Banghart, Edita Navratilova, William Birdsong

Pain is a multifaceted, psychological construct that involves extensive cortical processing. Cortex not only processes both sensory/discriminative and affective/motivational aspects of pain perception but can also shape ascending noxious signals through top-down control of the descending pain modulatory pathway.

This symposium will highlight emerging topics in cortical pain processing, including roles for endogenous opioids in persistent pain affect, synaptic mechanisms of opioidergic modulation, circuit mechanisms of negative pain affect generation, and neural pathways supporting placebo analgesia.

Matt Banghart (University of California San Diego, Co-Chair) will present studies using chemogenetics to uncover cortical pathways that engage the periaqueductal gray (PAG) during placebo analgesia in mice. His presentation will highlight similarities and differences in the circuitry underlying the analgesia produced by systemic morphine and morphine-conditioned placebo.

Edita Navratilova (University of Arizona) will present work on the anatomy of ACC mu and kappa opioid receptor (MOR and KOR) circuits and on the role of the MOR and KOR activity in pain. These behavioral pharmacology studies will highlight opposing analgesic and pronociceptive effects of MOR and KOR signaling during ongoing neuropathic pain.

Finally, Will Birdsong (University of Michigan, Co-Chair) will present synaptic physiology studies of thalamo-cortico-striatal pathways that are modulated by opioids in the ACC and discuss how endogenous and exogenous opioid agonists may induce opposing effects on neurotransmission in pain-related circuits.

Together, these presentations will provide diverse perspectives on the multitude of roles played by cortex in processing information elicited by noxious sensory stimuli to shape pain perception and analgesia.

PANEL • WEDNESDAY • 4:30 P.M. – 6:30 P.M. • SALON D

Novel Regulatory Pathways for Neuronal Protein Synthesis

Chair: Leonard Kaczmarek

Presenters: Shannon Farris, Elizabeth Jonas, Sulagna Das, Leonard Kaczmarek

The synthesis of proteins in neurons depends on incoming patterns of stimulation from the environment and from synaptic inputs. Activity-dependent translation of mRNAs in neurons is required for learning and memory and differs from that in many other cells types in that it produces changes in local morphology and connectivity that persist months or years after the original stimulus. This panel will give an overview of mechanisms that regulate RNA translation in neurons. Shannon Farris will describe how neurons that undergo different types of synaptic plasticity localize and translate different sets of

mRNAs in their dendrites. She will provide evidence that a significant subset of the translated mRNAs in dendrites are those that regulate mitochondrial function, implicating a key role for these organelles in neuronal plasticity.

Elizabeth Jonas will describe the relationship between mitochondrial function and local protein translation in neurons. She will describe how the function of the mitochondrial ATP synthase is altered by loss of the Fragile X Mental Retardation Protein, an mRNA-binding protein required for activity-dependent translation. and how this, in turn, regulates synaptic plasticity.

Sulagna Das will discuss how consolidation of short-lived synaptic proteins, important for memory, occurs at the post-synaptic terminal by undergoing cycles of transcription and local translation. By imaging individual Arc mRNAs and their translation status over time, she will elucidate the regulatory mechanisms by which activity-driven changes in gene expression are sustained in neurons.

Finally, Len Kaczmarek will describe how a potassium channel (KCNT1) is linked directly to proteins that regulate mRNA translation and how channel activation stimulates local translation of actin mRNA. He will also describe genetic mutations in the channel that over-stimulate local actin synthesis and result in severe intellectual disability and several different forms of epilepsy.

PANEL • WEDNESDAY • 4:30 P.M. – 6:30 P.M. • SALON E

Homeostatic Plasticity and Sleep in Autism Spectrum Disorders

Chair: Stephen Smith

Presenters: Lucia Peixoto, Carolyn Jones, Graham Diering, Stephen Smith

Sleep problems are among the most common and impactful comorbid feature of Autism Spectrum Disorders (ASD), present in up to 86% of individuals on the spectrum and heavily affecting the quality of life of individuals and their caregivers.

Sleep disruptions may simultaneously reflect underlying abnormalities in neurodevelopment, and cause further behavioral and biochemical disruptions by preventing normal sleep-associated plasticity. In this panel, we examine the linkages between disrupted plasticity and disrupted sleep in the context of autism.

Lucia Peixoto will discuss sleep ontogenesis in the typical mouse brain and the development of sleep problems in a genetic mouse model of ASD, Shank3ΔC. This mutation recapitulates the clinical ASD sleep phenotype and leads to an unusual response to sleep deprivation, including a worsening of the effect of sleep loss on cortical gene expression. She will show that in Shank3ΔC mice, problems falling asleep and unusual features in the EEG emerge during developmental critical periods of plasticity.

Carolyn Jones will present a prairie vole rodent model of juvenile sleep disruption that recapitulates, in wildtype prairie voles, features of sleep reported in ASD. Dr. Jones will describe longitudinal effects of early life sleep disruption on social interactions, behavioral flexibility, and sleep EEG.

Graham Diering will show that early life sleep disruption is indeed causative of lasting changes in behavior in genetically vulnerable Shank3ΔC heterozygous mice. Using quantitative proteomics, we also show that developing mice have profoundly different

responses to sleep deprivation in comparison to adults.
Stephen Smith will discuss plasticity-dependent protein-protein interaction networks in mouse genetic models of ASD. In ASD, networks appear "pre-scaled", which reduces the dynamic range of the system upon plasticity induction and may occlude normal homeostatic adjustments in synaptic strength, such as those occurring during sleep.

PANEL • WEDNESDAY • 4:30 P.M. – 6:30 P.M. • WANDERLUST

Peripheral Signals Suggest Central Targets for the Treatment of Drug and Alcohol Addiction

Chair: Kyle Frantz

Presenters: Kyle Frantz, Laura O'Dell, Lorenzo Leggio, Joshua Brown

In the quest for effective treatment of substance use disorders, new medication targets may be revealed by investigating how peripheral signaling molecules influence central reward circuits. Kyle Frantz (PhD, Georgia State University) will kick off by exploring the gut-brain axis in cocaine self-administration and cue-induced reinstatement after abstinence in rats. Correlational studies in adult males suggest bacterial populations that could predict cocaine vulnerability, whereas mechanistic analyses show that gut microbes may help regulate reinstatement in adult males (but not adolescents), potentially through gut-to-brain signaling molecules such as short-chain fatty acids. Laura O'Dell (PhD, University of Texas El Paso) will discuss how insulin-associated metabolic proteins contribute to enhanced nicotine intake in rodent models of diabetes. Her presentation will highlight sex differences in diabetes/insulin resistance and their intersections with central reward processing and behavior, with emphasis on reducing nicotine use in persons with metabolic disorders. Lorenzo Leggio (MD,PhD, NIDA and NIAAA) will address the role of feeding pathways in addictive behaviors, concentrating on the gut hormones ghrelin and glucagon-like peptide-1 (GLP-1) as potential therapeutics for alcohol and opioid use disorders. He will include rodent work using transgenic approaches and behavioral pharmacology, as well as translational studies with patients. Joshua Brown (MD, PhD, Brown University) will speak on his collaborative research with Carolina Haass-Koffler (PharmD, Brown University), which considers the anatomical and functional relationships between neuroendocrine pathways and noradrenergic activation during stressful events. In human laboratory studies with individuals with substance use disorders, she is integrating preclinical paradigms and pharmacological probes to evaluate potential targets in the development of new medications to treat addictive disorders. Together the panelists will suggest future directions for basic and clinical research.

PANEL • WEDNESDAY • 4:30 P.M. – 6:30 P.M. • ZIEGLER

Novel Insights Into Brain Functions Through Tissue Clearing and Whole-Brain Light-Sheet Imaging

Chair: Alexander Smith

Presenters: Samuel Centanni, Ashley Cunningham, Alexander Smith

Recent advances in tissue clearing and light-sheet microscopy techniques have allowed examination of protein expression and neurocircuitry throughout the entire brain in a

high-throughput, unbiased manner. These techniques have provided novel insights into previously under-studied brain regions and allow examination of neurocircuitry at an unprecedented scale. This panel will present exciting new data using these innovative approaches to study diverse neurobiological questions. First, Samuel Centanni (Wake Forest University) will present data mapping inputs and outputs of the insular cortex, and how this unbiased mapping led to the characterization of a motor cortex-insula-BNST pathway that controls stress coping behavior. Ashley Cunningham (Icahn School of Medicine at Mount Sinai) will then present data examining whole-brain histone serotonylation, a highly novel epigenetic histone modification, throughout the course of development. Finally, Alexander Smith (Medical University of South Carolina) will present data examining whole-brain activity patterns following cue-induced reinstatement of oxycodone seeking, and discovery of novel regions that are highly correlated with relapse-like behavior. Together, this panel will demonstrate the utility of tissue clearing techniques and light-sheet microscopy as a holistic approach for examining the brain, and highlight how these approaches can be used to rigorously examine a broad variety of neurobiological questions in a high-throughput, unbiased manner.

WEDNESDAY EVENING PANEL SESSIONS

PANEL • WEDNESDAY • 7:00 P.M. – 8:30 P.M. • INDEPENDENCE AUDITORIUM

An Open Science Approach to High Resolution, Comprehensive Atlases of Human Brain Morphology

Chair: Marek Kubicki

Presenters: Marek Kubicki, Nikos Makris

The past decade has brought the rapid development of more precise MRI acquisition and analytic tools that allow for investigating brain structure in-vivo. This rapid advancement, however, has not been mirrored by the development and refinement of manually curated neuroanatomy atlases. The process of manually segmenting a brain is not only time and labor-intensive, but also restricted to a few laboratories with access to expert neuroanatomists and custom-made closed-source labeling tools. Moreover, neuroanatomical definitions may vary from expert to expert depending on preferred conventions and are seldom explicit, which prevents the broader community from replicating or augmenting atlas creation procedures. Finally, definitions may also change as better data become available, but there is no process to modify atlases and manual segmentation protocols and keep track of changes.

The goal of this panel is to present an open science framework to parcellate brain structures, linking regional segments to explicit and commonly-used ontology incorporating ease of use in publicly-available software. We will present labeling protocols that are rooted in the legacy work of the Center for Morphometric Analysis used to create the Harvard Oxford Atlas. These protocols are being updated based on recent developments in cross species neural systems conceptualization and characterization, and used to label high resolution MRI. Importantly, the data set will be freely available to the community and distributed through the Open Anatomy Project, an open source, web-based atlas exploration system.

The panel includes Chair (Dr. Marek Kubicki, from Harvard Medical School) and three presenters. Dr. Kubicki's presentation, titled "MR Brain Atlases: from Neuroanatomy to Applied Morphometry" will cover the topic of how MR morphometric brain atlases are generated based on neuroanatomical knowledge, and how they are currently used in research and diagnostics. Dr. Nikos Makris (Center for Morphometric Analysis, Massachusetts General Hospital), in his talk titled "How Human is Human Connectional Neuroanatomy", will discuss how our knowledge of the human brain anatomy, especially connectional anatomy is still extremely limited and derived from non-human experimental models.

SHORT COURSE • WEDNESDAY • 7:00 P.M. – 8:30 P.M. • SALON B

Supervised Machine Learning for the Unsupervised Behavioral Neuroscientist

Chair: Simon Nilsson

Presenters: Ann Kennedy, Simon Nilsson, Kevin Coffey

Aberrant behavior is a core feature of many neuropsychiatric disorders, yet the study of complex behavior in freely moving rodents is relatively infrequently incorporated into preclinical models. This likely contributes to limited translational impact. A major bottleneck for the adoption of complex, ethology-rich, preclinical procedures are the technical limitations for consistently annotating detailed behavioral repertoires. Manual annotation is subjective, prone to observer drift, and extremely time-intensive. Commercial approaches are expensive and inferior to manual annotation. To overcome these issues, there has been a concerted effort by the behavioral neuroscience community to develop and adopt open-source machine-learning platforms for the automated analysis of preclinical behaviors.

In this short course, we will hear from three experts in the field who have developed fully open-source platforms for the automated analysis of behavior, spanning social interactions to ultrasonic vocalizations. Panelists will be introduced by Dr. Sam Golden, who will also moderate the panel discussion following individual presentations.

Dr. Ann Kennedy will present "MARS and Bento: open-source tools for behavior data analysis and visualization", highlighting the methodological approaches and benefits of automated supervised behavioral classification paired with high-fidelity neural recording datasets.

Dr. Simon Nilsson will present "Simple Behavioral Analysis (SimBA) – an open-source toolkit for computer classification of complex social behaviors in experimental animals", focusing on emerging computational approaches for the quantification and standardization of machine learning behavioral classifiers between research groups.

Dr. Kevin Coffey will present "The sound of silence: a guide to open-source software for ultrasonic vocalization (USV) analysis featuring DeepSqueak", focusing on the use machine vision approaches for the automated analysis of USV and unraveling their role in the subjective experiences of research rodents.

Short course participants will leave this panel with an introductory understanding of the caveats and benefits of open-source machine learning pipelines, and a general pulse for the future directions of this field.

PANEL • WEDNESDAY • 7:00 P.M. – 8:30 P.M. • SALON C

New Developments on Novel Circuits That Govern Responses to Threat and Safety

Chair: Jason Radley

Presenters: Heidi Meyer, Ryan Lalumiere, Jason Radley

How organisms respond and adapt to threats in their environment is fundamentally important for survival and has clinical implications for understanding a variety of psychiatric disorders. This panel will discuss recent work on the neurobiological systems underlying both the responses and adaptations to threats. First, Dr. Jason Radley will highlight recent studies on the impact of altering activity in a prefrontal–bed nuclei of the stria terminalis circuit on memory accuracy and generalization. His data suggest that increasing pathway activity following inhibitory avoidance training enhances discrimination between similar contexts, whereas disrupting activity shifts responses toward generalization. Next, Dr. Heidi Meyer will discuss research investigating how the ventral hippocampus primes responding during conditions of threat and safety. Her findings indicate that the ventral hippocampal projection to the prelimbic medial prefrontal cortex exhibits progressive reductions in neural activity across discriminative threat conditioning, while elevated activity in these neurons facilitates the active inhibition of threat behavior. Dr. Ryan LaLumiere will discuss recent work indicating that the basolateral amygdala selectively influences spatial and contextual memory consolidation via projections to the medial entorhinal cortex. Moreover, the findings indicate that pathway stimulation at 8 Hz is particularly important for enhance such memories and that such stimulation influences activity-regulated cytoskeletal element protein in downstream brain regions in a sex-dependent manner. Dr. Jason Radley will highlight recent studies on the impact of altering activity in a prefrontal–bed nuclei of the stria terminalis circuit on memory accuracy and generalization. His data show that increasing pathway activity following inhibitory avoidance training enhances discrimination between similar contexts, whereas disrupting activity shifts responses toward generalization. Together, the findings presented in this panel will provide new insights into how different circuits critically regulate divergent behaviors in response to threats and safety.

PANEL • WEDNESDAY • 7:00 P.M. – 8:30 P.M. • SALON D

Neural Activity-Dependent Approaches for Molecular and Cellular Characterization of Neuronal Ensembles in Reward Memories

Chair: James Otis

Presenters: Marine Salery, James Otis

During drug taking, substance abusers learn to associate cues with the rewarding effects of drugs, and these cues repeatedly guide them back to drug taking and relapse. Learned associations are encoded within sparse patterns of neurons called neuronal ensembles, which can be identified by increased intracellular calcium or IEG expression. We will

describe molecular and cellular characteristics of neuronal ensembles in relapse to reward seeking. Marine Salery (Mount Sinai, NY) will describe endogenous reactivation of cocaine-activated ensemble neurons in nucleus accumbens of Arc-CreERT2 mice following CPP training and optogenetic experiments to assess their role in behavior, as well as single nuclei RNA sequencing experiments to assess transcriptional profiles of the reactivated ensembles. James Otis (MUSC) will describe the characterization, longitudinal tracking and functional interrogation of ensembles in dorsal mPFC and midline thalamic areas that govern heroin seeking in mice. He uses two-photon calcium imaging to track activity dynamics of ensemble neurons and optogenetics to identify their functional roles in heroin-seeking. Understanding the molecular and cellular mechanisms of ensembles mediating addiction-related memories will allow specific disruption of these maladaptive learned behaviors.

PANEL • WEDNESDAY • 7:00 P.M. – 8:30 P.M. • SALON E

Linking the Pain Experience to the Body: From the Brain to a Yard Sale of Bodily Systems

Chair: Vitaly Napadow

Presenters: Patrick Finan, Robert Edwards, Vitaly Napadow

The pain experience is encoded in conscious awareness by the brain. However, it is not divorced from the body and distinct visceral, immune, and musculoskeletal systems. The experience of pain can be regulated by descending inhibitory and facilitatory pathways in the brainstem, as well as sensory, affective, and cognitive processing in the brain, interacting with bodily systems that are also engaged by pain comorbidities like opioid misuse, sleep disturbance, and affective dysregulation. Here, we will explore these clinically-relevant biobehavioral interactions, noting potential therapies that tap into interoceptive and neurovisceral pathways to combat chronic pain. Such research considers human psychobiology to better understand the links between pain experience and the body. Presentations by Drs. Finan and Edwards will cover the rich linkage between pain and the immune system, as both pro- and anti-inflammatory humoral mediators are known to up- and down-regulate nociceptive pathways. This complex association may be maintained by an array of pain-related factors assessed in their clinical and experimental paradigms, including sleep, affective function, and pain-related cognition. Dr. Napadow will then report his neuroimaging and psychophysiological research investigating the mechanisms supporting applied therapies, such as transcutaneous vagus nerve stimulation, that tap into brain-body pathways integral to interoception, emotion regulation, and self-referential processing to modulate pain circuitries. These presentations will detail the myriad pathways by which pain interacts with specific visceral, interoceptive, and immune systems, thereby informing potential novel therapies for analgesia.

PANEL • WEDNESDAY • 7:00 P.M. – 8:30 P.M. • ZIEGLER

Oh, the Places You'll Go

Chair: Elora Williams

Presenters: Jared Smith, Drew Duglan, Zoe McElligott

Neuroscience has become increasingly popular. Indeed, the number of universities across the United States offering neuroscience programs, with the majority of them granting doctoral degrees, has drastically increased [1]. Unfortunately, the influx of trainees has not equaled an increase in tenure-track positions. Between 1981 to 2013, the number of faculty positions in biomedical fields grew by 150%, where the number of new PhDs expanded 278% [2]. In another study, the rate of PhDs awarded in science and engineering was seven times greater than the rate of newly available faculty positions [3]. In 2013, only 20% of those with postdoc experience held tenured track positions, indicating the importance of discussing career options outside of this canonical career in science [2].

Acknowledging occupational options post-PhD is imperative for the continuation of contributions to science and innovation. Here, each panelist will discuss their own pathway through science and provide insight on how to best prepare for the diverse choices available. Dr. Smith has experience working as a postdoc in two different labs, receiving a K99 award, and now as a senior scientist at a highly translational gene therapy company (RegenXBio Inc). Dr. Duglan communicated his way from postdoc researcher to scientific liaison at a world-renowned non-profit organization (Scripps Research). Dr. McElligot is an Assistant Professor within the Department of Psychiatry at the University of North Carolina at Chapel Hill and will discuss the challenges and opportunities within university research. Elora Williams, PhD candidate, will provide the introductory comments and moderate the discussion.

References:

1. Rochon et al (2019).
2. Kahn S and Ginther DK. (2017)
3. Schillebeeckx et al. (2013)

THURSDAY, FEBRUARY 3, 2022

THURSDAY MORNING PANEL SESSIONS

PANEL • THURSDAY • 7:30 A.M. – 9:30 A.M. • INDEPENDENCE AUDITORIUM

Sex-Differences in Aging From Sleep, Pain, Brain Circuitry and Disease States

Chairs: Josee Guindon, John Lawrence

Presenters: Josee Guindon, Holly Hunsberger, Natalie Ebner, John Lawrence

Aging and age-related diseases are associated with a myriad of environmental and genetic factors. These factors collectively determine risks for accelerated aging and diseases such as Alzheimer's Disease (AD)-related dementias. These factors, such as sleep disturbance,

toxicity-induced inflammatory processes, sex and hormonal status, and nutritional state contribute to aging diseases and AD susceptibility, underscoring the importance of studying these factors to discover effective therapeutic interventions. This panel gathers scientific expertise spanning from behavioral, molecular, cellular, synaptic, neuroimaging, and clinical findings. We will discuss novel concepts and discoveries in aging diseases from sleep disturbance, sex differences, pain, and brain circuitry using a wide range of current technologies (behavioral pharmacology, biochemistry, transcriptomics, metabolomics, machine learning, immunohistochemistry, patch clamp electrophysiology, optogenetics, and other techniques). Dr. Guindon, as Chair, will share her recent research findings on sex differences in aging mice following chronic pain models and discuss how physiological and pain markers might influence these differences. Dr. Hunsberger will discuss sex differences in sleep patterns, sundowning behavior, and neural activity throughout AD progression using an activity-dependent mouse line. Dr. Ebner will present novel behavioral and neuroimaging evidence from her clinical trials on single-dose and chronic intranasal oxytocin administration towards functional benefits (cognition, affiliative processes, pain, etc) in aging. Finally, Dr. Lawrence, as co-Chair, will discuss roles of retinoic acid deficiency in aging and AD through the comprehensive examination of post-mortem human AD transcriptomics, sex-specific circuit changes, and gene expression alterations in mouse models of AD, and propose a working hypothesis of how these molecular and circuit changes alter hippocampal learning as a result of retinoic acid deficiency. This panel will reveal new discoveries and treatments in aging diseases such as AD, with a special emphasis on sex-differences and brain circuits.

PANEL • THURSDAY • 7:30 A.M. – 9:30 A.M. • SALON B

Bringing Polysubstance Use in From the Cold: Novel Clinical and Pre-Clinical Data on a Neglected Topic

Chair: Lori Knackstedt

Presenters: Lara Ray, Lori Knackstedt, Courtney Wilkinson, Mohamed Kabbaj

The majority of substance users engage in polysubstance use (PSU), consuming more than one drug simultaneously, sequentially or concurrently. Despite the prevalence and deleterious consequences of PSU, its behavioral and neurobiological underpinnings remain largely unknown. This panel describes novel brain and behavioral data from both human and rodent studies of PSU. Lara Ray, PhD (UCLA) will describe patterns of alcohol, psychostimulant, cannabinoid, and opioid co-use in clinical human samples. Evaluation of substitution, complimentary, and alternative explanations of co-use patterns will be discussed. Lori Knackstedt, PhD (UF) will present data from rat models of intravenous self-administration which find that access to oral alcohol after intravenous cocaine or oxycodone self-administration alters anxiety during withdrawal, demand for drug, reinstatement of drug-seeking, and the neurobiology underlying the reinstatement of drug-seeking. Courtney Wilkinson (UF) will present data from a rat model of oral oxcycodone and alcohol co-consumption. Interactions between anxiety, drug intake, and the ability of oxytocin to reduce alcohol intake in this PSU model will be described. Mohamed Kabbaj (FSU) will present data from a rodent model of ketamine-alcohol PSU which finds individual and sex differences in the ability of alcohol to alter ketamine

self-administration. He will also describe the effects of ketamine-alcohol PSU on structural plasticity in the nucleus accumbens, with assessments of dendritic spine morphology. Altogether, the panel's findings indicate that PSU alters the motivation to seek drugs, withdrawal-associated anxiety, and neurobiology. The consideration of such effects is essential for the understanding of drug-seeking and the development of novel pharmacotherapies to reduce drug seeking.

PANEL • THURSDAY • 7:30 A.M. – 9:30 A.M. • SALON C

Losing Appetite Over Stress? Circuit Mechanisms Mediating the Reciprocal Interaction Between Emotions and Feeding Behavior

Chair: Candice Contet

Presenters: Jeffery Dunning, Qingchun Tong, Sarah Stern, Yunlei Yang

The majority of individuals diagnosed with an eating disorder also suffer from a co-existing psychiatric condition, such as anxiety, depression or addiction, suggesting a shared etiology. Accordingly, identifying the neurobiological mechanisms driving this overlap is an active area of investigation. Some neuronal populations known to be involved in the regulation of appetite are now appearing to respond to stress or to influence emotional behavior as well. Conversely, signaling molecules and circuits known to modulate stress responses or aggression have emerged as critical regulators of metabolism and food intake. This panel will delve into these pathways to shed light on putative mechanisms underlying the high co-morbidity of eating and affective disorders. First, Dr. Jeff Dunning will focus on the parasubthalamic nucleus, a brain region known to respond to aversive stimuli, and discuss the role of neurons characterized by distinct connectivity, molecular markers, or sensitivity to stress in the motivation to feed and drink. Dr. Qingchun Tong will then discuss the circuit from the paraventricular hypothalamus, a typical feeding center, to the lateral septum, a known aggression center, that co-regulates stress-related behaviors and feeding-related metabolism. Next, Dr. Sarah Stern will share how she used unbiased transcriptomic methods to identify a population of neurotensin neurons in the lateral septum that link stress to restrictive feeding behavior. Finally, Dr. Yunlei Yang will decipher novel oxytocin-mediated neural circuits for anxiety and anorexia using a combination of neurophysiology, genetics, and behavioral assays of motivation. Altogether, these panelists will introduce new preclinical data highlighting recent advances in our understanding of the mechanisms causing the co-occurrence of maladaptive feeding behaviors and negative emotionality. Dr. Candice Contet will lead discussion of the presentations.

PANEL • THURSDAY • 7:30 A.M. – 9:30 A.M. • SALON D

Establishing Brain-Behavior Relationships With Neuromodulation

Chair: Nolan Williams

Presenters: Colleen Hanlon, Jonathan Downar, Nolan Williams, Noah Philip

Non-invasive neuromodulatory technologies are developing rapidly across clinical neuroscience. The availability of new approaches, coupled with increased knowledge of underlying neurocircuitry relevant to psychiatric illness, sets the stage of innovative new clinical interventions.

This symposium will highlight four novel and unpublished advances that demonstrate the potential of TBS as a new clinical intervention across the psychiatric spectrum. Colleen Hanlon (Wake Forest) will present on translational and clinical studies involving mPFC stimulation; Jonathan Downar (Toronto University Health Network) will present data used to secure an FDA clearance for theta-burst stimulation for depression; Nolan Williams (Stanford University) will present on an accelerated rTMS approach to rapidly reduce neuropsychiatric symptoms such as depression and suicidal ideation. Noah Philip (Brown University/Providence VA) will describe results from the first sham-controlled study of iTBS for posttraumatic stress disorder, describing results related to clinical and functional improvement and resting-state functional neuroimaging predictors of response.

Taken together, these presentations will demonstrate the broad, near-term potential for neuromodulation applicable across a broad range of neuropsychiatric diseases. It is our hope this session will prompt further discussion about new methods to engage targets of interest, and how to leverage these new technologies in clinically meaningful ways.

PANEL • THURSDAY • 7:30 A.M. – 9:30 A.M. • SALON E

Endogenous Opioid Systems: Redundant or Specialized?

Chair: Lakshmi Devi

Presenters: Ivone Gomes, Manoj Puthenveedu, Elyssa Margolis, Lin Tian

The endogenous opioid system has often been considered highly redundant: the peptides bind promiscuously to the receptors in the opioid family, the receptors generally activate the same signaling pathways, and opioid agonist actions in various brain regions are sufficient to mimic the behavioral effects of systemic opioid administration. On the other hand, recent studies and emerging techniques are beginning to resolve important features that indicate more sophisticated properties and organization. In this panel we will highlight new tools and insights from subcellular to intact brain resolution. Devi will briefly introduce the context of the session. Gomes will present evidence generated in cell culture models that endogenous opioid peptides are not redundant, but instead each peptide has unique binding and activity profiles. Further, she will highlight endogenous opioid peptides that are high potency, selective ligands for opioid receptor heteromers. Pruthenveedu will discuss the distinct spatiotemporal profiles of signaling driven by endogenous opioid peptides. Specifically, he will describe how different peptides drive distinct trafficking fates, subcellular localization patterns, and signaling profiles of opioid

receptors. Margolis will describe electrophysiological studies in ventral tegmental area neurons interrogating the neural responses to different endogenous opioid peptides, providing evidence for promiscuity in signaling in some cases and highly selective responses in other cases. Finally, Tian will describe new tools for detecting endogenous opioid peptide release in vivo. Enabling the characterization of the temporal dynamics of extracellular endogenous opioid peptides during behavior provides the greater context for understanding when and where the phenomena described earlier in the session may be instantiated. Together these talks begin to build a new framework for our understanding of the function and dynamics of the endogenous opioid systems.

PANEL • THURSDAY • 7:30 A.M. – 9:30 A.M. • WANDERLUST

Computational Psychiatry Insights into Dimensional Processes

Chairs: Peter Hitchcock, Amrita Lamba

Presenters: Amrita Lamba, Frederike Petzschner, Melissa Sharpe, Peter Hitchcock

The clinical sciences are undergoing a conceptual renaissance. One key initiative, exemplified by the RDoC framework, is to identify algorithmic and neural dimensions of psychiatric illness that cut across diagnostic criteria and range over the lifespan. One promising dimension is perseveration—the extent to which an individual engages in rigid thinking and repetitive behavior, particularly concerning experienced or anticipated negative events. The first two presentations will suggest that responding differently to losses vs. gains may fuel rumination and worry and concurrently impair adaptive decision making. Peter Hitchcock will present on the neurocomputational mechanisms of self-judgment. He will also show that rumination disrupts trial-and-error learning needed for effective behavior. He will discuss how both mechanisms may transact with life stressors and influence the onset and maintenance of depression. Rachel Bedder will present research suggesting that people who are less saddened by sad events than gladdened by happy events may be paradoxically susceptible to anhedonia. She will present evidence linking anticipatory thinking with biased choice perception and propose neural mechanisms through which such bias influences value-encoding brain regions. The last two presentations will establish brain-behavior links between neuromodulatory mechanism, functionally relevant neural pathways, and perseverative tendencies. Amrita Lamba will present evidence suggesting that anxious individuals have difficultly disengaging from a previously adaptive behavior as it becomes increasingly unrewarding. Amrita will then present evidence that reduced learning in anxiety is accompanied by a blunted pupil-linked arousal response, suggesting that anxiety-related behavioral inflexibility may arise through dampened norepinephrine signaling of uncertainty. The panel will conclude with Matilde Vaghi, who will present evidence that functional and structural alterations within fronto-striatal circuits underlie persistent thoughts in individuals with OCD. Matilde will then discuss evidence showing that early-adolescent individual differences in compulsivity is linked to atypical developmental trajectories of cortico-striatal systems.

PANEL • THURSDAY • 7:30 A.M. – 9:30 A.M. • ZIEGLER

Sex Differences in Dopamine Signaling and Behavior

Chair: Matthew Wanat

Presenters: Brooke Bender, Matthew Wanat, Jill Becker, Erin Calipari

The mesolimbic dopamine system plays a central role in decision making, learning, and motivated behaviors. Dopamine neuron activity and dopamine release in the striatum can differ between males and females. These sex differences in dopamine transmission can arise from differences in hormonal regulation as well as from underlying basal differences between male and female subjects. This panel will highlight recent behavioral, neurochemical, and mechanistic findings on sex differences in dopamine release and dopamine-dependent behavior. Brooke Bender (University of Pittsburgh) will present findings on sex differences in the effects of intermittent cocaine self-administration on addiction-like behavior, including motivation for cocaine, compulsive and habit-like cocaine seeking, and Pavlovian cocaine-cue associations. Matt Wanat (University of Texas-San Antonio) will present findings on sex differences in conditioned responding and reward-evoked dopamine release during Pavlovian learning. Jill Becker (University of Michigan) will present findings on the effects of selective estradiol receptor activation, in the striatum, on dopamine release and motivation for reward in males and females. Erin Calipari (Vanderbilt) will present findings on hormonal regulation of nucleus accumbens microcircuitry and show how estradiol alters cholinergic regulation of dopamine release in females through actions at nicotinic acetylcholine receptors. Collectively this panel will highlight how sex differences and the hormonal regulation of dopamine transmission can manifest across wide array of behaviors.

THURSDAY AFTERNOON PANEL SESSIONS

PANEL • THURSDAY • 4:30 P.M. – 6:30 P.M. • INDEPENDENCE AUDITORIUM

Function and Dysfunction in the Bed Nucleus of the Stria Terminalis

Chair: Katie Yoest

Presenters: Joanna Dabrowska, Lindsay Halladay, Zoe McElligott, Katie Yoest

The bed nucleus of the stria terminalis (BNST) is a heterogenous brain region that is well situated to act as a central node within circuitry involved in diverse behaviors. In particular, the BNST is unique in its ability to regulate behaviors related to both aversive and appetitive states, via both parallel and overlapping neural circuits. This has made the BNST an attractive target for understanding the neural underpinnings of psychiatric diagnoses, which are often characterized by alterations in both stress and reward processes. In this panel we will present studies highlighting the range of behaviors that are regulated by the BNST. First, Dr. Joanna Dabrowska (Rosalind Franklin University) will present data showing how oxytocin facilitates cued fear learning via cell-type specific modulation of the dorsolateral BNST and inhibition of outputs to the central amygdala. Then, Dr. Lindsay

Halladay (Santa Clara University) will present work showing that manipulating BNST activity can both mitigate and recapitulate socio-emotional deficits associated with early life stress. Next, Dr. Zoe McElligott (University of North Carolina-Chapel Hill) will discuss sex differences in acute and protracted opioid withdrawal, as well as sex differences in GABAergic signaling in the BNST during acute opioid withdrawal. Finally, Dr. Katie Yoest (Michigan State University) will discuss how sex differences in the organization of the oxytocin system in the posterior BNST - where males have three-fold greater expression of oxytocin receptors - are related to the sex-specific regulation of social behavior in juvenile rats. This session, specifically featuring work from female scientists, demonstrates how the BNST can regulate both reward processes like social interaction and socio-emotional development, and aversion, in the form of fear learning and opioid withdrawal.

PANEL • THURSDAY • 4:30 P.M. – 6:30 P.M. • SALON B

Neural Pathways and Molecular Mechanisms Underlying Relapse Behavior and Drug Craving

Chair: Kathryn Reissner

Presenters: Charlotte Bavley, Kathryn Reissner, Michael Stefanik

The ongoing addiction crisis has only gotten worse since the onset of the Covid-19 pandemic. One of the contributing factors to the discouragingly high relapse rates for individuals living with substance use disorders is the craving produced by re-exposure to cues previously associated with drug use. Drug craving was added as a criterion to diagnose substance use disorder in the most recent iteration of the DSM, demonstrating its perceived relevance and contribution to the disease. Both clinical and preclinical studies have shown that cue-induced drug craving intensifies over the course of abstinence – a phenomenon aptly termed incubation of craving. Few therapeutic approaches have successfully incorporated the mitigation of drug craving as part of treatments for substance use disorders. With the advancement of available tools to dissect and manipulate specific neural circuits and genetically-defined cell types in the brain, we now have unique opportunities to better understand the time-dependent mechanisms that contribute to the development of drug craving and increased likelihood of relapse. This represents a critical step to improving treatment options available given the highly heterogeneous nature of brain cells and the complexity of neural pathways that contribute to relapse-like behaviors. This panel will focus on studies that combine animal models of addiction with cutting edge circuit- and cell type-specific approaches to gain a better understanding of the mechanisms underlying the incubation of drug craving and relapse-related behaviors. Dr. Charlotte Bavley will present findings delineating the cell-type specific transcriptomic signatures of D1 and D2 cells in the nucleus accumbens following chronic heroin consumption and either short or extended abstinence in rats. Dr. Kathryn Reissner will discuss studies designed to assess transcriptomic responses of nucleus accumbens astrocytes during early and late abstinence from cocaine self-administration. Dr. Michael Stefanik's research explores the long-lasting neuroadaptations that result from chronic consumption of psychostimulants and opioids using multi-pronged approaches. Dr. Wendy Lynch will present ongoing studies examining the efficacy of pharmacotherapeutics in diminishing

drug craving and relapse behavior in order to better understand and improve currently available options for individuals living with substance use disorders. She will also discuss how these effects vary following short- versus extended-access drug self-administration and following short versus protracted abstinence.

PANEL • THURSDAY • 4:30 P.M. – 6:30 P.M. • SALON C

Central Neural Bases for Normal/Abnormal Hearing and Auditory Behaviors

Chairs: Li Zhang, Shaowen Bao

Presenters: Qiaojie Xiong, Alfonso Junior Apicella, Patrick Kanold, Fan-Gang Zeng

This panel aims at discussing our current understanding of the neural bases for central auditory processing in normal conditions and in hearing disorders. The panel will consist of two parts, with the first part focusing on the latest explorations of the neural circuits for auditory perception and behaviors, and the second part focusing on neural bases for deficits of information processing in several auditory disorders. In the first part, Dr. Xiong (Cold Spring Harbor laboratories) will first present findings on the role of the striatum in auditory frequency discrimination in mice with a specific emphasis on dopamine modulation. Dr. Apicella (UT San Antonio) will then discuss contributions of the auditory cortex to emotional behaviors. Led by Dr. Zhang (U Southern California), the panel will further discuss the general logic for auditory circuits, related to ascending, descending, canonical, or noncanonical circuits, underlying the generation of auditory perception and behaviors. In the second part, Dr. Kanold (Johns Hopkins) will first talk about how aging alters the circuits and population activity in auditory cortex, and then Dr. Fan-Gang Zeng (UC Irvine) will discuss human studies on the neural basis and perceptual consequences of tinnitus. Finally, led by Dr. Bao (U of Arizona), the panel will further discuss the noise-induced hearing deficits and cortical mechanisms. Together, we hope these presentations will provide an overview of multifaceted research approaches and current understandings of normal and abnormal auditory processing, which may lead to the development of new research strategies to address these long-held outstanding questions in the auditory field.

PANEL • THURSDAY • 4:30 P.M. – 6:30 P.M. • SALON D

Using Human Cells and Tissue to Interrogate Genetic Mechanisms of Risk in Schizophrenia

Chair: Thomas Hyde

Presenters: Brady Maher, Euan Parnell

The last decade has seen an explosion in our understanding of the genetic underpinnings of major psychiatric disorders. The challenge now is to understand the pathophysiological mechanisms that link a specific genomic locus and clinical symptoms. This task is complicated by the fact that these pathophysiological processes may map to specific cellular populations and/or developmental timepoints. Studies in human neuronal cells and

tissues afford the unique opportunity to study specific types of cellular populations, in order to identify the abnormalities that increase risk of illness. This panel will outline how the use of human cells and tissue enables researchers to interrogate the genetic mechanisms underlying psychiatric disorders.

Tom Hyde (Lieber Institute for Brain Development) will discuss findings from laser-capture microdissection of granule cells within the dentate gyrus of human brain within the context of schizophrenia.

Brady Maher (Lieber Institute for Brain Development) will demonstrate how deep characterization of patient- and control-derived iPSCs, stratified based on polygenic risk for schizophrenia, can be used to define molecular and cellular correlates of clinical phenotypes.

Finally, Euan Parnell (Northwestern) will discuss his studies of on the 16p11.2 duplication copy number variant in iPSC derived neurons. He will show how excitatory and inhibitory iPSC-derived neuronal cultures can be used to look at early dysfunction in schizophrenia, and the potential contribution of calcium dysfunction to this disorder.

PANEL • THURSDAY • 4:30 P.M. – 6:30 P.M. • SALON E

The Role of Intrinsic and Extrinsic Factors on Perineuronal Nets and Associated Neuronal Plasticity

Chairs: Amy Lasek, Carol Dannenhoffer

Presenters: Carol Dannenhoffer, Katherine Conant, Travis Brown, Amy Lasek

Perineuronal nets (PNNs) are lattice-like extracellular matrix structures that form during brain development. In the cortex they predominantly surround parvalbumin-expressing GABAergic interneurons. PNNs regulate neuronal activity and synaptic plasticity and protect neurons from oxidative stress, cluster neurotransmitter receptors, and sequester growth factors. Recent research has demonstrated that many intrinsic and extrinsic factors can alter the structure of PNNs. This panel will delve into the function of PNNs and their responses to drugs, diet, and circadian rhythms, and relate these changes to altered plasticity, excitatory/inhibitory balance in the cortex, and feeding, depression and addiction. Dr. Amy Lasek, an Associate Professor at the University of Illinois at Chicago, will chair the session and provide introductory comments. Dr. Carol Dannenhoffer, a Postdoctoral Research Associate at the University of North Carolina at Chapel Hill, will present on the long-term consequences of adolescent intermittent ethanol exposure on PNNs in the prefrontal cortex of adult rats. Her findings will highlight the persistent changes induced by alcohol during a critical window of prefrontal cortical development and relate them to addiction-relevant behavioral phenotypes that result from adolescent alcohol exposure. Dr. Katherine Conant, a Professor at Georgetown University, will present her work on the effect of stress and antidepressants on PNNs and matrix metalloproteinase 9, an endopeptidase that cleaves extracellular matrix proteins. Associated changes in excitatory/inhibitory balance in the cortex will be discussed. This work has implications for major depressive disorder and the response to antidepressant treatment. Dr. Travis Brown, an Associate Professor at Washington State University, will present his results demonstrating alterations in cortical PNNs in standard laboratory rats

and obesity-susceptible and -resistant rats consuming a high fat diet. Sex differences in PNN responses will be discussed and results will be integrated with the effect of high fat diet on dendritic spine density in the prefrontal cortex. This research has implications for motivation, cognitive control of food consumption, and obesity and weight-loss. Dr. Amy Lasek will conclude the panel by presenting results of her research demonstrating sex differences in perineuronal nets in the insular cortex and insular cortex activity during aversion-resistant ethanol consumption. She will also show data demonstrating sex differences in aversion-resistant ethanol consumption in response to enzymatic disruption of PNNs and chemogenetic inhibition of PV neurons in the insular cortex. These studies provide insight into brain mechanisms of compulsive drinking, a hallmark of alcohol use disorder.

PANEL • THURSDAY • 4:30 P.M. – 6:30 P.M. • ZIEGLER

The Evolution of Neurotrauma Research: Past to Present

Chair: Cole Vonder Haar

Presenters: Akiva Cohen, Kris Martens, Adam Bachstetter, Audrey Lafrenaye

Traumatic brain injury (TBI) is a major health concern, with over 2.8 million recorded annually in the US. Despite years of study, little progress has been made on the development of therapeutics. This is, in part, due to the complex pathophysiological and functional consequences that emerge across the early to chronic post-injury phase. The panel will take a historical perspective on methodology as it applies to the study of TBI. Specifically, each speaker will detail advantages and disadvantages of historical approaches and then contrast them with modern methods which are being applied to better understand TBI. Cole Vonder Haar (Ohio State University) will serve as the chair and provide introductory remarks. Akiva Cohen (University of Pennsylvania) will discuss neuronal dysfunction and how the use of extracellular and intracellular recording in live brain slices together with in vivo recording has led to understanding alterations in hippocampal circuitry caused by mild TBI that underlie and contribute to cognitive impairments associated with concussion. Kris Martens (Ohio State University) will focus on high-resolution operant cognitive-behavioral methods and how they may be used to better understand pathology-function links for chronic TBI outcomes. Adam Bachstetter (University of Kentucky) will describe advances in pharmacological and genetic approaches to study cytokine signaling mechanisms regulating the neuroinflammatory processes after a TBI. Audrey Lafrenaye (Virginia Commonwealth University) will discuss the evolution of quantitative histological and biomarker assessments in the context astrocyte and olikgodendrocyte alterations/pathologies following neurotrauma. At the conclusion of these presentations, audience members will have an appreciation for how methods have evolved and how current methods may be applied to better understand TBI.

PANEL • FRIDAY • 7:30 A.M. – 9:30 A.M. • INDEPENDENCE AUDITORIUM

Extrasynaptic Proteolysis as a Key to Understanding Physiological and Aberrant Synaptic Plasticity

Chair: Elizabeth Quinlan

Presenters: Leszek Kaczmarek, Katherine Conant, Elizabeth Quinlan, Iryna Ethell

Understanding synaptic physiology and pathology requires incorporation of perisynaptic extracellular matrix signaling. We will show that perisynaptic proteolysis induces pre- and postsynaptic signaling cascades, the dysregulation of synaptic stability and aberrant structural and functional plasticity in age and disease. Recent advances identify the extracellular matrix metalloproteinase MMP-9 as a novel and critical effector in 1) the etiology of epilepsy, schizophrenia and addiction 2) mediation of antidepressant efficacy 3) the rejuvenation of plasticity in adults and 4) structural and functional deficits in Fragile X Syndrome. These insights are enabled by novel tools to track MMP9 activity including sensors for large scale visualization in whole-brain, FRET-based biomarkers for longitudinal in vivo tracking and clinically relevant EEG measures. Dysregulation of MMP-9 is implicated in the emergence and reoccurrence of epilepsy, the efficacy of clinically prescribed anti-depressants, and the delusional symptoms of schizophrenia. MMP-9 gene polymorphisms are also found in major psychiatric disorders. Therapeutically, activation of MMP-9 promotes recovery of vision in models of amblyopia, and active clinical trials show that MMP-9 inhibitors reverse the deficits in Fragile X Syndrome. We will highlight the active and instructive role of perisynaptic MMP9 signaling in sculpting changes in synaptic structure and function. Leszek Kaczmarek will describe how MMP-9 controls structural and functional synaptic plasticity in epileptogenesis, alcohol addiction and schizophrenia. Katherine Conant will describe the critical role played by MMP-9 in the efficacy of anti-depressant treatments. Elizabeth Quinlan will show that the threshold for the induction of perisynaptic MMP-9 is labile is lowered by sensory deprivation. Iryna Ethell will show that excessive MMP-9 activity contributes to the development of sensory hypersensitivity in FXS by regulating perineuronal nets.

PANEL • FRIDAY • 7:30 A.M. – 9:30 A.M. • SALON C

Maladaptive Decision-Making in Health and Disease: Rodent and Human Studies

Chair: Cole Vonder Haar

Presenters: Donna Calu, Cole Vonder Haar, Mariya Cherkasova, Jared Young

Decision-making is a fundamental process for organisms. This may be as simple as the decision to immediately avoid an aversive stimulus or may involve complicated long-term costs and benefits which must be weighed. Maladaptive decision-making (i.e., those that result in lower long-term utility) is often associated with a variety of psychiatric and neurological disorders. These impairments manifest in a variety of ways across diseases, including inherent preference for risk, reduced aversion to loss, or insensitivity to changing outcomes. Despite the importance, the fundamental neural substrates of maladaptive choices are still not fully understood. The current panel will describe multiple approaches to understanding decision-making, with a focus on the power of experimental manipulations and data modeling to understand how these processes may be modified and understood. Donna Calu (University of Maryland-Baltimore) will describe how individual differences in behavioral flexibility of rats relate to drug relapse vulnerabilities that persist despite negative consequences. Cole Vonder Haar (Ohio State University) will discuss how brain injury fundamentally changes probabilistic decision-making in rats using a high-resolution dataset (N = 120) collected across multiple studies. Mariya Cherkasova (West Virginia University) will discuss the risk-promoting effects of reward-paired cues in humans - also seen in rodents - and how these effects may promote loss-chasing in slot machine gamblers. Jared Young (University of California-San Diego) will describe the effects of long-term cannabinoid exposure on risk-based decision-making in a mouse model of bipolar disorder. At the conclusion of these presentations, audience members will understand how decision-making may be studied in the context of human disorders, how these may be modeled at the animal level, and how data analytic techniques may help interpret the biological underpinnings of these processes.

PANEL • FRIDAY • 7:30 A.M. – 9:30 A.M. • SALON D

Mechanisms and Alterations in Inhibitory GPCR Signaling

Chair: Chris Ford

Presenters: Joseph Lebowitz, Chris Ford, Kim Neve, Brian Muntean

Inhibitory Gi/o-coupled GPCRs regulate multiple neural circuits in the basal ganglia and mesolimbic system via pre- and post-synaptic neuromodulatory actions. In this panel speakers will discuss recent work examining the mechanisms by which inhibitory GPCRs signal and mediate transmission, with a focus on identifying alterations in receptor signaling cascades that potentially contribute to behavioral alterations associated with these systems. Joe Lebowitz (Vollum Institute) will discuss the role of the vesicular Ca2+ sensor synaptotagmin-1 in somatodendritic dopamine signaling. Chris Ford (University of

Colorado) will speak about recent work examining how alterations in D2-receptor mediated G-protein signaling induced by repeated cocaine exposure alters the sensitivity of D2-receptor signaling which in turn drives drug seeking behaviors. Kim Neve (Portland VA Medical Center) will discuss the effect of pathogenic variants of the human dopamine D2 receptor on receptor function in vitro and in vivo. He will describe the effects of the mutations on arrestin binding, G protein activation, downstream signaling pathways, and behavior. Brian Muntean (Augusta University) will focus on the essential role of the signal transducer Gao in choreographing motor coordination by tuning cell-type specific cAMP responses to neuromodulatory signals.

PANEL • FRIDAY • 7:30 A.M. – 9:30 A.M. • SALON E

Consequences of Alcohol Exposure From Adolescence to Senescence

Chair: Fulton Crews

Presenters: Fulton Crews, Victoria Macht, Kati Healey, S. Alex Marshall

Recent studies suggest that age impacts the consequences of alcohol use. This panel will present studies on the long-lasting impact of adolescent, adult, and senescent alcohol exposure. Dr. Fulton Crews, Bowles Center for Alcohol Studies-UNC, will present studies on adolescent intermittent ethanol (AIE) exposure inducing long lasting increases in HMGB1-TLR-RAGE signaling leading to epigenetic silencing of forebrain cholinergic neuron genes and loss of cholinergic neurons and associated reversal learning deficits. Victoria Macht, University of North Carolina at Chapel Hill, will present on the long-term impact of AIE on adult hippocampal neurogenesis and neuroimmune gene induction in male and female rats that alters adult cognition and other behaviors. Studies reversing adult pathology using galantamine and indomethacin provide insight into the mechanisms of persistent pathology. Kati Healey, Duke University, will discuss how AIE causes persistent adult alterations of the glial-neuronal tripartite synaptic structure within the hippocampus and prefrontal regions. She will present data finding AIE exposure reduces astrocyte-synaptic connectivity, with no effect on astrocyte morphology, and that these deficits are reversable with gabapentin (Neurontin). Alex Marshall, North Carolina Central University, will focus on alcohol-induced neuroinflammation and neurodegeneration in senescence. He will present data on the impact of aging on microglia, cytokines, neuronal loss and responses to alcohol using non-dependent alcohol binge drinking as well as alcohol dependence inducting models. These studies explore the impact of young and old ages on ethanol induced persistent neuronal, glial, and epigenetic mechanisms of behavioral pathology.

PANEL • FRIDAY • 7:30 A.M. – 9:30 A.M. • ZIEGLER

Black Diamonds to White Lines: Exploring the Effects of Stress on Drug-Seeking Behavior

Chair: Kayla Siletti

Presenters: Kayla Siletti, Kyle Brown, Jayme McReynolds, Marek Schwendt

Stress is an unavoidable feature of life that can profoundly interfere with learning and decision-making. For those dependent on drugs of abuse, uncontrollable stress can drive similarly uncontrollable drug cravings that ultimately lead to relapse. While the notion of stress-precipitated drug craving is widely accepted, there is notable diversity in the outcomes of stress on drug-seeking. Stress-induced drug-seeking is dependent on a number of variables, including characteristics of the stress experience (e.g. chronicity, controllability, and severity), the extent of prior drug exposure (e.g. limited versus prolonged access), and sex, to name just a few. This panel will highlight the importance of diversity in models of stress-induced drug-seeking. Kayla Siletti will present data from a conflict model of cocaine self-administration. Her studies explore the effects of environmental stress and the contributions of striatal D1DR and D2DR expressing neuronal populations on drug-seeking and -taking under conditions of uncertainty and ambivalence. Using a paradigm that contrasts single exposure to either escapable or inescapable physical stress, Dr. Kyle Brown will discuss the role of stressor controllability training on the incubation of cocaine and oxycodone seeking during abstinence. Next, Dr. Jayme McReynolds will present a model of stress-induced escalation of cocaine seeking. This work will demonstrate stress-induced changes in not only reinstatement of cocaine-seeking but also stress reactivity and affective and social cognitive behaviors. In contrast to the aforementioned physical stressors, Dr. Marek Schwendt will introduce predator scent stress as a preclinical model of PTSD. Utilizing this model, he will discuss whether differential stress phenotype predicts methamphetamine-seeking and c-fos neural activity patterns in female rats.

FRIDAY AFTERNOON PANEL SESSIONS

PANEL • FRIDAY • 4:30 P.M. – 6:30 P.M. • INDEPENDENCE AUDITORIUM

Behavioral Responses to Noxious Stimuli: How the Brain Promotes Survival Through Coping Mechanisms

Chair: David Barker

Presenters: Nicolas Massaly, Michael Baratta, David Barker, Flavia Barbano

Protective behavioral responses to pain or stress occur naturally and increase the chances of survival of the organism to maintain the species. By using newly developed tools, unexpected findings concerning how certain brain circuits modulate responses to noxious stimuli are emerging, reshaping our concepts on the role played by several brain structures and their connectivity. This symposium highlights some of those novel findings: Dr. Nicolas Massaly (Washington University in St.Louis) will present data on pain-induced

cellular adaptations within the nucleus accumbens dynorphin projections to the lateral hypothalamic area and their role in mediating the aversiveness of acute and persistent pain; Dr. Michael Baratta (University of Colorado, Boulder) will present findings implicating specific medial prefrontal circuits in behavioral control over stress (a key aspect of coping), findings that further demonstrate that an initial experience of behavioral control reduces subsequent fear conditioning and, when given after fear conditioning, accelerates later fear extinction and prevents spontaneous recovery. Dr. David Barker (Rutgers University) will talk about the processing of nociceptive stimuli by neurons of the lateral preoptic area that project to the ventral tegmental area and their role in predicting nociceptive outcomes, as well as the synaptic connectivity supporting this signaling; and Dr. Flavia Barbano (National Institute on Drug Abuse) will discuss the unexpected role of glutamatergic neurons of the ventral tegmental area in response to threatening stimuli that drive innate defensive behavior. Understanding the biology and neurocircuitry of behavioral responses to noxious stimuli is essential to identify system malfunctioning that could lead to neuropsychiatric disorders. Given the massive social and economic costs in terms of suicide, health care and decreased productivity associated with neuropsychiatric disorders, it becomes evident that a deeper awareness of how a dysregulated copying system may lead to illness is imperative.

PANEL • FRIDAY • 4:30 P.M. – 6:30 P.M. • SALON C

Novel Neurobiological Mechanisms Underlying Neuronal Maintenance and Degeneration

Chair: Hui-Chen Lu

Presenters: Warren Hirst, Hui Zhang, Caiwei Guo, Yimin Zou, Hui-Chen Lu,

Neurodegeneration occurs in various neurological disorders including Alzheimer's disease (AD), Huntington's disease, Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). As our population continues to age, these diseases are increasing in prevalence and taking a staggering social and financial toll on our society. Thus, it is of critical importance that we innovate new strategies to prevent or slow the progression of these devastating and inexorably fatal diseases. It is not only critical to elucidate the molecular pathways underlying the pathology of human neurodegenerative diseases but also to understand how active maintenance programs sustain brain function during healthy aging. Dr. Warren Hirst (Biogen) will start this panel by introducing our current knowledge on the genetic basis of PD and genetic links with PD pathophysiology including lysosomal dysfunction, endosomal trafficking, mitochondrial quality control and immune response. He will present the opportunities and challenges of developing novel therapeutics to these targets and how they are linking familial and sporadic forms of PD in preclinical research and clinical development. Dr. Hui Zhang (TJU) will show how mutations, such as R1441G, in the LRRK2 gene, the most prevalent cause of familial and sporadic PD, results in synaptic dysfunction, energy failure and axonal degeneration in an age-dependent manner, and why sSNc neurons are specifically susceptible to neurodegeneration. Dr. Caiwei Guo (Stanford) will talk about the mechanisms of ALS. Variants in the pre-synaptic gene UNC13A are one of the strongest genetic risk factors for ALS and the Gitler laboratory's new discovery on how the most common ALS pathology (TDP-43 nuclear depletion) causes cryptic exon splicing and dysfunction of UNC13A. Dr. Yimin Zou (UCSD) will discuss the recently

discovered role of the planar polarity signaling components in the maintenance of glutamatergic synapses in the adult brain. He will also talk about new evidence that amyloid beta oligomers cause synapse degeneration and memory impairment by directly targeting the planar polarity components in the synapses. Dr. Hui-Chen Lu (IUB) will talk about how NMNAT2, the key NAD synthesizing enzyme in the brain, maintains neuronal health. In particular, she will describe the critical roles of NMNAT2 in axonal transport and how NMNAT2 modulates energy homeostasis in axons of glutamatergic neurons. This panel will demonstrate the utility of a diversity of approaches in pursuit of a greater understanding of the pathobiology of neurodegenerative diseases, and active neuronal maintenance mechanism in healthy brains with the promise that this knowledge will be instrumental in designing new therapeutic approaches to prevent or treat neurodegenerative diseases.

PANEL • FRIDAY • 4:30 P.M. – 6:30 P.M. • SALON D

Opioid Regulation of Glutamate Signaling and Behavior

Chair: Dillon McGovern

Presenters: Dillon McGovern, Anna Kruyer, Giuseppe Giannotti

Ventral tegmental area (VTA) GABA neurons regulate dopamine neuron activity via a local projection modulated by the mu-opioid receptor. This canonical circuit has been directly linked to opioid seeking and relapse behavior. However, within the last decade it has become clear that both cortical and midbrain glutamatergic circuits influence opioid behavior and neuronal signaling. This panel will present novel data that elucidates the importance of circuit specific glutamate neurotransmission during opioid-seeking behavior. Dillon McGovern, a 4th year PhD candidate in the Root Lab, will present his work investigating a subset of VTA neurons, defined by the presence of the vesicular glutamate transporter 2, and their modulation by opioids as well as their involvement in oxycodone self-administration and cued reinstatement. Dr. Anna Kruyer, a research assistant professor in the Kalivas lab, will present her data that reveals circuit specific astroglia modification following heroin reinstatement, including that drug-associated cues increase glutamate release in the nucleus accumbens core to stimulate heroin seeking and elevate astrocyte proximity to D2-MSN synapses. Lastly, Dr. Giannotti, a postdoctoral fellow in the Peters lab, will close the session with his data evaluating the paraventricular thalamus to accumbens circuits in heroin self-administration and relapse. In combination this work greatly extends what is currently understood about circuit specific glutamatergic modulation following opioid use and reinstatement as well as expands previously established opioid-related circuitries to provide a more thorough understanding of the neural circuits that underlie opioid signaling and behavior.

Transcriptomic Tools and Molecular Methods for Neural Circuit Dissection in Nonhuman Primates

Chairs: Mark Eldridge, Peter Rudebeck

Presenters: William Stauffer, Adriana Galvan, J. Megan Fredericks, Vincent Costa

Recent experiments employing molecular methods are revolutionizing our approach to the study of systems neuroscience in nonhuman primates and offer a glimpse of the high-precision clinical tools of the future. This collection of talks will reveal a blueprint for how complementary cutting-edge transcriptomic and molecular techniques can be combined to reveal the detailed mechanics of how neural circuits modulate behaviour.

Dr Bill Stauffer (University of Pittsburg) will explain how he has used a transcriptomic analysis to define new classifications for cell types in the rhesus monkey striatum – a region of the brain implicated in Parkinson's, Tourettes, and many other neurological disorders. Dr Stauffer has leveraged the transcriptomic fingerprints of these newly defined cell types to create viral vectors with enhancers that confer cell-type specificity. These vectors will allow for the targeted delivery of molecular tools for modulating neural activity.

Dr Adriana Galvan (Emory University) will present data characterizing a new chemogenetic tool for suppressing neural activity in nonhuman primates. Dr Galvan has performed an electrophysiological assessment of the 'PSAM/PSEM' chemogenetic system, and a pharmacokinetic analysis of its activating ligands in rhesus monkeys. A major advantage of this system is that it can be activated by the FDA-approved drug, varenicline (Chantix), which should aid its translation to humans.

Ms Megan Fredericks (Icahn School of Medicine at Mt Sinai) will demonstrate how pathway-specific chemogenetic tools, DREADDs, can be used to modify behavior in rhesus macaques. Using an intersectional virus approach, Ms Fredericks will report that inhibiting neurons in basolateral amygdala that project to the ventral prefrontal cortex disrupts probabilistic stimulus reward learning.

Dr Vincent Costa (OHSU) will explain how he has used a transcriptomic analysis to define new classifications for cell types in the rhesus monkey amygdala – a region of the brain implicated in anxiety and mood disorders.

Ascending and Descending the Slopes of Prefrontal Pyramidal Neurons in Addiction

Chair: Jacqueline McGinty

Presenters: Susan Ferguson, Elizabeth Doncheck, Nicholas Graziane, Saurabh Kokane

Dysregulation of the prefrontal cortex during addiction is a major characteristic of relapse to drug seeking. However, the major projection neurons of the prefrontal cortex (pyramidal neurons or PNs), differ according to their cortical layer, inputs and outputs, excitability, dendritic morphology, and gene expression. We do not know enough about these subsets of PNs or how they are dysregulated by addictive drugs. Do all PNs in layer V that project to the nucleus accumbens have a thick apical dendrite and express D2 dopamine receptors (D2drs)? Do addictive drugs affect D1-expressing PNs differently from those expressing D2 receptors? These questions and more will be addressed by a diverse panel of investigators who represent multi-disciplinary perspectives. Susan Ferguson (U WA) will discuss the role of two major subsets of corticostriatal projection neurons (intratelencephalic and pyramidal tract) in the behavioral and neuroplastic effects of cocaine as well as in risky decision-making. Elizabeth Doncheck (MUSC) will discuss in vivo calcium imaging data on the emerging activity dynamics and noradrenergic modulation of prelimbic cortical pyramidal neurons during heroin seeking. Nicholas Graziane (Penn State U) will discuss the effects of opioid withdrawal on the intrinsic and synaptic properties of Ddr-expressing thin-tufted and putative D2dr-expressing thick-tufted PNs in the anterior cingulate cortex (ACC) as well as how neuronal activity in the ACC regulates opioid withdrawal. Saurabh Kokane (MUSC) will discuss the effects of heroin abstinence on the intrinsic excitability and synaptic plasticity of PNs projecting to nucleus accumbens in D1dr- and D2dr-cre rats and their regulation by cAMP-dependent protein kinase A. Altogether this panel will highlight the importance of investigating the relationship of cell- and projection-specific subpopulations in the prefrontal cortex to preclinical models of addiction.

M1. Investigating the Effects of Social Housing Conditions on Social Behavior and Stimulated Dopamine Release in the Nucleus Accumbens

Ivette Gonzalez*, Brandon Luma, Noah Leonardo, Paras R. Patel, Daniel C. Jaklic, Cynthia A. Chestek, Jill B. Becker

Methamphetamine (METH) is a highly addictive stimulant. Factors like social isolation can contribute to the vulnerability in addiction to METH. Studies using cocaine self-administration have shown that housing with conspecific of the same sex attenuated motivation for cocaine in females but did not affect a male's motivation for cocaine. Previous studies with METH have shown that female's motivation for METH decreased when they had a social partner. However, there were individual differences, as some socially housed females had extremely high breaking points while others had very low breaking points. This study was conducted to understand individual differences, as well as the sex differences, in how social housing and social relationship behavior affects motivation for METH in females and males. The quality of the relationship between socially housed cage mates was examined. Social behaviors such as pinning, napping, and grooming were analyzed and used to determine dominance. Social behavior was recorded 2 weeks before the first exposure to METH. Animals were injected with METH (1.5 mg/kg IP) and returned to their home cage after the effects had worn off one hour later. Social behavior was then recorded the next day, at the beginning of the dark phase of the light cycle. Results showed that social play decreased after prior exposure of the dominant male to METH, while social play increased for females after the dominant female was previously treated with METH. Further studies need to be done to understand the extent that METH played a role in this effect. Data was also collected investigating dopamine (DA) release in the nucleus accumbens core and shell of socially housed and individually housed rats using fast scan cyclic voltammetry. A 16-channel carbon fiber electrode was lowered into the nucleus accumbens where peak DA was collected after electrical stimulation of the ventral tegmental area. Preliminary results showed that socially housed rats have a higher max DA than singly housed rats. The current data are being analyzed to better understand differences between the nucleus accumbens core and shell and whether it is affected by social housing conditions and biological sex.

M2. Evaluating the Role of mGlu3 Receptors in Post-Methamphetamine Motivational and Cognitive Deficits

Cassandra Modrak, Peter Hamor, Marek Schwendt*

Long-term methamphetamine (meth) abuse is associated with a spectrum of mild-to-severe neurobehavioral deficits, including changes in impulsivity, decision-making, and working memory (WM). Several studies suggest that impaired cognition predicts a higher risk of relapse and worsens treatment outcomes in chronic meth users. Moreover, both the severity of cognitive impairment and the intensity of meth craving seems to undergo

dynamic changes after discontinuation of meth use, giving rise to a high-risk period for recovering meth users. Unfortunately, the neurobiology underlying these behavioral deficits remains poorly understood. Here we introduce a translational animal model that allows for the concurrent evaluation of post-meth WM performance and meth-seeking. Further, we evaluated the effects of mGlu3 glutamate receptor activation on behavioral and neurochemical variables. mGlu3 is a viable target for intervention, as studies have shown that dysregulation of mGlu2/3 receptors is associated with WM deficit and persistent drug-seeking. Male Sprague-Dawley rats were first trained on the operant delayed match-to-sample (DMS) task and tested for 10 days to establish WM baseline across a range of delays (0-24s). Rats then underwent 6 days of 1 hr and 14 days of 6 hr meth self-administration followed by up to 7 weeks of homecage abstinence with repeated behavioral analysis. Re-testing on the DMS task revealed a post-meth WM deficit that coincided with robust meth-seeking. Next, indirect activation of mGlu3 via the glutamate carboxypeptidase II (GCPII) inhibitor 2-PMPA (30 mg/kg, i.p) rescued WM impairment at long delays in a subgroup of most severely-impaired rats. In contrast, 2-PMPA treatment did not have an effect on cue/context-primed meth-seeking. In addition, long term changes in WM performance or extinction learning were not observed in rats previously treated with 2-PMPA or vehicle. Finally, under a condition of high WM demand (DMS task with a single 24s delay), 2-PMPA-treated rats showed a trend towards performance improvement indicating immediate pro-cognitive effects of mGlu3 activation. Utilizing this model, further studies will investigate possible sex differences in post-meth cognitive performance and involvement of mGlu3 in neurobiological mechanisms underlying meth-seeking and WM.

M3. Using LabGym to Categorize and Quantify Complex Rodent Behaviors

Carrie Ferrario, Yujia Hu, Bing Ye*

The careful analysis of behavior is central to studying a wide range of motivated behaviors like feeding and drug-seeking, neuropsychiatric disease, and their potential treatments. For decades we have relied on observational approaches to examine key features of behavior both qualitatively and quantitatively. At the heart of this approach is operationally defining behavioral features and then having an individual count their occurrences or rate their intensity. This is labor intensive and can be variable across individuals, research labs, time, etc. Recent advancements in machine-learning algorithms, particularly those based on deep learning, have opened new avenues to examining behavior. For example, computational tools that track body part position are useful for determining motor patterns. While this can provide detailed information about position in space (e.g., grasping movements or locomotion) it is challenging to extract information about behavioral features that are more complex -- i.e., those that are defined not just by one movement, but by several different movements, and/or by the quality of those movements. For example, psychostimulant drugs like amphetamine produce a range of behaviors from locomotion at low doses to more complex and intermixed behaviors emerge as dose is increased (e.g., rearing, darting, and repetitive, stereotyped behaviors), which are collectively referred to as psychomotor activity. These complex behaviors are more challenging to measure using approaches that track body position. LabGym is a recently developed approach that uses a novel deep neural network to evaluate both the spatiotemporal details and to categorize and quantify complex patterns of animal behavior. Here we describe and evaluate the ability of LabGym to measure the psychomotor-activating effects of amphetamine, spontaneous behaviors (e.g., eating, grooming, etc) to provide a platform for continued development of novel approaches to behavioral analysis.

M4. A Novel Ph-Sensitive Optical Reporter Reveals Compartmentalized Trafficking of the Dopamine Transporter in Neurons

Pingyue Pan, Jacqueline Saenz, Xiaofeng Zhou, David Barker, Emanuel Dicicco-Bloom*

The dopamine transporter (DAT) is a major gateway for DA uptake and termination of dopaminergic signaling in the brain. While much of our understanding of DAT trafficking came from studies of heterologous cells, it remains unclear if central DA neurons, especially their dendrites and axons, share the same rules. We have now engineered a novel pH-sensitive reporter for DAT by conjugating pHluorin to the second exofacial loop of human DAT. We show that DAT-pHluorin is a superior tool to study DAT trafficking in neurons as it exhibits DA uptake, cocaine sensitivity, as well as regulated DAT recycling like the endogenous protein. Using DAT-pHluorin we show that intracellular DAT is primarily found in the soma and dendrites, while axons express most of the DAT on the plasma membrane. Additionally, we observed higher fractions of acidic DAT in axonal varicosities as compared to axonal shafts, which indicates that axonal varicosities may be active sites of DAT turnover in the axon. Furthermore, our data suggests that cocaine redistributes neuronal DAT from the soma to the neurites in a stepwise process. Thus, our study using the newly engineered DAT optical reporter reveals, for the first time, compartmentalized DAT trafficking rules in neurons.

M5. Pharmacological Manipulation of Kv7 (KCNQ) Channels in Cultured Striatal Neurons Affects Electrophysiological Excitability

Emily Jorgensen, Robert Phillips, Jeremy J. Day*

KCNQ “m-type” K+ currents are important for controlling neuronal excitability, serving as a brake against hyperexcitable states in the nervous system. As such, changes in KCNQ channel expression and activity have been implicated in several neuropsychiatric disorders including epilepsy, mood disorders, and substance abuse. KCNQ channels in the nucleus accumbens are altered by chronic ethanol consumption and that KCNQ channels and D2 receptors are functionally coupled, resulting in escalated drinking behaviors in rodents. To better understand the function of KCNQ channels in the striatum, we used a high-density multielectrode array (MEA) recording system to measure single-neuron electrophysiological activity from rat primary striatal neuron cultures. Neurons were harvested from embryonic day 18 striatal tissue, and MEA recordings were performed at DIV 12 with pharmacological manipulation of KCNQ channels. Following a 20 min baseline, we administered the KCNQ agonist, flupirtine maleate (3 μM and 30 μM), and KCNQ antagonist, XE-991 (1 μM and 10 μM), in addition to vehicle controls. We found a dose-dependent effect with both pharmacological reagents. KCNQ antagonism produced a heterogeneous effect on neuronal action potential frequency, with 10 μM XE-991 significantly decreasing spike frequency in one cell population while increasing activity in a separate population. In contrast, KCNQ stimulation with flupirtine maleate increased activity in a small population of cells at 3 μM, but severely decreased activity in ~50% of cells at the higher concentration of 30 μM. These results suggest that KCNQ channel manipulations produce divergent responses in distinct cell populations, and have potential

relevance for understanding drug-mediated changes in KCNQ expression and function. Future projects will use gene-editing techniques to manipulate KCNQ levels in striatal neurons to further identify how KCNQ channels influence striatal neuron excitability.

M6. An Atlas of Transcriptionally Defined Cell Types in the Rat Ventral Tegmental Area

Robert Phillips, Jennifer Tuscher, Emma Andraka, Samantha Black, Lara Ianov, Jeremy Day*

The ventral tegmental area (VTA) is a complex brain region that is essential for reward function but is also implicated in neuropsychiatric diseases including substance abuse. While decades of research on VTA function have focused on the role of dopaminergic neurons, recent evidence has identified critical roles for VTA GABAergic and glutamatergic neurons in reward processes as well. Interestingly, molecular characterization has revealed that subsets of these neurons express genes involved in the transport, synthesis, and vesicular packaging of multiple neurotransmitters, providing evidence for co-release neurons. However, these studies have largely relied on low-throughput methods, and the molecular architecture of the VTA has not been comprehensively examined. Here, we performed single nucleus RNA-sequencing (snRNA-seq) on 21,600 VTA cells from male and female Sprague-Dawley rats to generate a transcriptional atlas of the rat VTA. We identified 16 transcriptionally distinct cell types within the VTA, including 7 neuronal populations. Further subclustering revealed several VTA neuronal populations expressing markers for more than one neurotransmitter system, with one cluster exhibiting high expression levels of genes involved in the synthesis and transport of GABA, glutamate, and dopamine. Finally, snRNA-seq enabled the de novo identification of thousands of marker genes for each transcriptionally distinct population, revealing cluster-specific enrichment of gene sets implicated in neuropsychiatric and neurodevelopmental disorders, as well as specific phenotypes associated with alcohol and tobacco use. Together, these results highlight the heterogeneity of cellular populations in the VTA and identify novel markers and disease-linked genes enriched in distinct neuronal subtypes.

M7. Epigenome Editing of Nucleus Accumbens Cell Subtype Transcripts Regulated by Fentanyl Abstinence

Makeda Turner, Eric Choi, Ramesh Chandra, Seth Ament, Megan Fox, Mary Kay Lobo*

In recent years, the opioid use epidemic has significantly impacted societal health burdens around the world. This is in part due to the ease at which synthetic opioids like fentanyl are obtained resulting in an increase in opioid overdoses. Many studies indicate that dysfunctionality in the mesocorticolimbic brain areas are central to understanding opioid use, dependence, and addiction. The nucleus accumbens (NAc) is a critical brain hub for altered molecular processes mediating behavioral responses to opioids and other used substances. Therefore, understanding the molecular and transcriptional programs of the neuronal subtypes within the NAc deserve considerable and critical attention. Our lab has performed cell subtype specific translatome profiling in the two NAc projection neuron subtypes- dopamine receptor 1 and 2 expressing medium spiny neurons (D1- and

D2-MSNs) after prolonged abstinence from repeated fentanyl exposure. We identified distinct MSN subtype gene expression networks that are altered during fentanyl abstinence including hub genes, which are key drivers of gene expression alterations in MSN subtype specific modules. To build on this, we are developing CRISPR epigenome editing tools that will target specific hub genes in MSN subtype modules that are significantly regulated by fentanyl abstinence- 5 days 10µg/ml fentanyl followed by 10 days of abstinence. Since most genes are down-regulated we use CRISPRa (activation) to upregulate expression of hub genes in MSN subtypes. Using a two-vector adeno-associated virus (AAV) system we designed single gRNA or multiplex gRNAs, the latter targeting multiple hub genes within one module. gRNAs targeting hub genes or a lacZ control gRNA are cloned into an AAV-gRNA-NLSGFP, which allows expression of nuclear GFP. The second vector is an AAV-DIO-dCas9-VP64 containing the nuclease dead Cas9 fused to the VP64 transcriptional activation domain. We have transfected these vectors along with Cre into Neuro2A cells and demonstrated upregulation of MSN subtype fentanyl abstinence regulated hub genes. We are currently packaging these vectors into AAVs to target NAc MSN subtypes, using D1-Cre and A2A-Cre mice, during opioid exposure and abstinence to determine if upregulating hub genes can influence MSN subtype/fentanyl abstinence gene expression networks.

M8. Transcriptomic Adaptations in Emotional and Sensory Brain Nuclei in Perinatal Fentanyl Exposed Rodents

Jimmy Olusakin, Gautam Kumar, Catherine Haga, Megan Fox, Mahashweta Basu, Makeda Turner, Jason Alipio, Cali Calarco, Asaf Keller, Seth Ament, Mary Kay Lobo*

Since the early 2000s, there has been an increase in opioid consumption within the US, including among pregnant women. Use of the synthetic opioid fentanyl has increased ~300% within the last decade. However, little is known about the molecular mechanisms underlying fentanyl use particularly during brain development. Using a rodent model of perinatal fentanyl exposure, we previously demonstrated a lasting emotional and sensory deficit at adolescent and adult ages, consistent with human findings. In the present study, our aim is to understand the neurobiological mechanisms occurring with developmental fentanyl exposure. We use a Multi-omic sequencing approach to investigate the transcriptional programs dysregulated in fentanyl use in a brain tissue specific manner. Fentanyl was administered in drinking water of pregnant dams from embryonic day 0 through gestational periods until weaning at P21. Tissue punches were collected from 5 brain areas from juvenile aged mice (~P35) and processed for RNA-sequencing. Brain regions analyzed include emotional/reward brain regions: nucleus accumbens (NAc), ventral tegmental area (VTA), prelimbic (PrL) region of the prefrontal cortex and sensory brain regions: primary somatosensory cortex (S1) and ventrobasal (VB) thalamus. These experiments were performed in both sexes as we had observed sex differences in some of the lasting behaviors. We identified differentially expressed gene sets, and performed enrichment analysis, weighted gene coexpression network analysis (WGCNA), and upstream transcription factor analysis. We observed sex driven differences in differentially expressed gene sets within all brain regions analyzed. We identified upstream transcriptional programs and hub genes that could mediate the lasting behavioral changes

in fentanyl use. Collectively, our studies are identifying unique gene expression adaptations across multiple brain regions relevant for lasting behaviors observed in perinatal fentanyl exposed mice.

M9. Capturing and Profiling Cocaine-Recruited Neuronal Ensembles in the Nucleus Accumbens

Marine Salery, Arthur Godino, Yu Qing Xu, John F. Fullard, Panos Roussos, Eric J. Nestler*

Learned associations between the rewarding effects of drugs and the context in which they are experienced are decisive for precipitating drug-seeking and relapse in addiction. These associative memories are stored in sparse and highly discriminative populations of concomitantly activated neurons that define drug-recruited neuronal ensembles. In this study, we explore the dynamics and molecular mechanisms of both the recruitment of these ensembles upon initial drug exposure and their contribution to the encoding, strengthening and ultimately the expression of drug-associated memories. A related goal is to define the intrinsic or acquired cellular properties favoring the allocation of specific cells to these functional ensembles and predict their further reactivation. Capitalizing on the activity-dependent neuronal labeling in Arc-CreERT2 mice (Denny et al., 2014), we were able to capture and permanently tag (fluorophores, channel-rhodopsin) cocaine-activated cells in the nucleus accumbens for further characterization, optogenetics, and nuclei sorting. We identified subsets of neurons activated at both early and late stages of drug exposure and show that the reactivation of an initial ensemble correlates with behavioral sensitization levels. Similarly, re-exposure to a cocaine-paired context in a conditioned place preference (CPP) paradigm triggered cocaine-recruited ensembles' reactivation. Using optogenetics-mediated artificial reactivation, we found that populations recruited at early versus late stages of drug exposure had opposite roles in CPP expression. Single nucleus RNA Sequencing was then performed on FACS-isolated tagged neurons, and we successfully isolated a cluster of reactivated cells within the initially activated ensemble. Together, this ensemble-specific approach represents a pivotal step in identifying highly specific cellular processes involved in the encoding of pathological memories associated with drug addiction.

M10. More than a Gut feeling: Cholecystokinin Afferents to the Nucleus Accumbens Encode Aversion and Modulate Dopamine Transmission

*Oliver Culver**

Originally known for its role in regulating GI physiology, cholecystokinin (CCK) is the most abundant neuro-modulatory peptide in the brain, and is highly expressed in brain regions that regulate emotional processing and motivational behavior. These include the medial prefrontal cortex (mPFC), basolateral amygdala (BLA), and ventral tegmental area (VTA). Using CCK-Cre mice crossed to reporter mice, we found that inescapable foot shock produces robust c-Fos expression preferentially in CCK+ neurons of the BLA, and VTA. Furthermore, using Cre-dependent viral expression of mCherry, we demonstrated that CCK+ BLA pyramidal neurons and CCK+ VTA dopamine neurons project to the nucleus accumbens (NAcc). Finally, bath application of CCK-8 (the most common form of

CCK in the brain) into nucleus accumbens slice preparations increases extracellular dopamine in the NAcc, as measured by the genetically encoded dopamine sensor dLight1.2. Overall, these data suggests that multiple distinct CCK+ projection neurons to the nucleus accumbens may play distinct roles in maladaptive behaviors associated with aversive processing and traumatic experience.

M11. The Relationship between Substance Use, Prior Trauma History, and Risk of Developing Post-Traumatic Stress Disorder in the Immediate Aftermath of Civilian Trauma

Felicia Gould, Mackenzie Jones, Philip Harvey, Lisa Reidy, Gabrielle Hodgins, Vasiliki Michopoulos, Jessica Maples-Keller, Barbara Rothbaum, Alex Rothbaum, Kerry Ressler, Charles Nemeroff*

Many reports have documented the relationship between post-traumatic stress disorder (PTSD) and substance use. Substance use is commonly comorbid with PTSD and is a risk factor for trauma exposure. The aim of this study was to prospectively examine how recent substance use, abuse, or dependence influenced the development of PTSD in the context of a prior trauma history, including child abuse, and the severity of initial trauma reactions. Participants (N=81) were recruited and assessed at the emergency department of a large urban hospital in Miami and serum levels of common drugs of abuse were measured. Although substance use appeared to be a risk factor for trauma exposure, neither self-reported nor blood toxicology influenced the development of PTSD. Positive toxicology screens were more likely to be associated with a diagnosis of substance abuse or dependence, $\chi2(1) = 4.11$, $p=0.04$. Participants with a history of physical abuse were more likely to have a positive toxicology screen, $\chi2(1) = 4.03$, $p=0.05$. The majority of our trauma-exposed subjects (66%) were found to be positive for one or more illicit substances at presentation at the ED.

M12. Neuropixels Recordings Reveal Distributed Signaling of Threat Probability and Threat-Elicited Behaviour Across Rodent Midbrain and Pons

Jasmin Strickland, Michael McDannald*

The generation of suitable threat signals in response to threat stimuli is generally considered to be the domain of the forebrain. These signals are then thought to be relayed to midbrain/pons regions to organize the behavioural aspects of fear and adaptive fear responding. Recording from the ventrolateral periaqueductal gray, a midbrain region commonly implicated in generating fear behavior, our lab has found signals for both threat probability and behavioural output. This suggests that threat probability signaling is not exclusive to forebrain regions. To more comprehensively map midbrain and pons threat signaling, we devised a system for multi-region, high-density recording using Neuropixels probes during a fear discrimination procedure in rats. The one-centimeter Neuropixels probe was implanted such that its path coursed through the superior colliculus, most periaqueductal gray subregions, all dorsal raphe subregions, median raphe and additional regions enroute. We recorded 1812 neurons across 21 regions from 10 rats. Analysis of firing during cue presentation showed that neurons could be clustered into discrete functional types, with each type distributed across at least several regions. Every

functional cluster showed a unique temporal pattern of differential cue firing. From these clusters, a small functional network emerged: consisting of clusters showing short latency firing increases to danger, strong differential firing of danger and safety with firing patterns tightly correlated across clusters. Regression revealed these neurons to initially and rapidly signal threat probability, then giving way to signaling of threat-elicited behaviour. Additional analysis of the period following the outcome indicates these regions also play a role in threat outcome and prediction error signals, expanding even further the potential role of midbrain/pons networks in threat signaling and behaviour. These results suggest that networks of midbrain/pons regions not only generate threat-elicited behaviour in response to threat stimuli, but may also play a role in the generation of threat signals themselves.

M13. Live versus Predatory Threat on Foraging by Bed Nucleus of the Stria Terminalis GABA Neurons

Annie Ly, Alexandra Barker, Emily Prevost, Dillon McGovern, David Root*

The motivation to venture outside a safe context in search for food, in spite of potential threats, is essential to survival. GABA neural activity in the bed nucleus of the stria terminalis (BNST), is implicated in stress and fear response. However, the underlying relationship between GABA BNST activity and changes in foraging behavior in response to a threat experience is unclear. Here, we compared changes in foraging behavior in response to a live or robotic predator threat. In addition, we utilized chemogenetic inhibition in order to investigate the role of GABA BNST activity in predatory threat response. Male and female VGaT::Cre mice received viral delivery of Cre-dependent FLEX-GFP or FLEX-hM4Di to the anteromedial BNST (AP+0.3,ML±0.6,DV-4.05). Mice were trained on a foraging task to search for food at discrete and incrementally greater distances in a brightly lit arena. After obtaining food, mice learned to retreat into a dark, enclosed “nest” safe context. The mice were then exposed to either a robotic land predator or a live predator positioned in front of a food source at the farthest distance. In our findings, both live and robotic predatory threat increased latency of successful foraging during the threat exposure itself. In the post-48 hour period after threat exposure, both robotic and live predator threat increased time spent in the safe context, which was decreased with chemogenetic inhibition of VGaT neurons in the BNST, but only after live predator exposure. The results demonstrate similarities between the effect of live and robotic predatory threat on foraging behavior during the threat itself but differential response in the 48 hours after the exposure and with silencing of GABA neurons within the BNST.

M14. Psychedelic-Induced Alterations in Central Amygdala Reactivity in Response to an Aversive Stimulus

Devin Effinger, Sema Quadir, Melissa Herman*

Psychedelic compounds have re-emerged as a potential treatment for affective psychiatric illnesses such as major depression disorder (MDD) and substance use disorder (SUD). Psilocybin, a pro-drug to the compound psilocin, is a hallucinogenic compound found in psilocybe cubensis mushrooms and is currently being explored in clinical trials. The central amygdala (CeA) is a primary region in the brain that receives input regarding internal and external arousal states and coordinates behavioral responses. CeA

dysregulation is associated with MDD and SUD, and psilocybin administration has been shown to reduce amygdala activity in clinical imaging studies. However, the specific circuit-based alterations responsible for this decreased activity are unknown. To investigate this, neuronal calcium dynamics were recorded using fiber photometry in conjunction with an aversive air puff stimulus. Recordings were collected for baseline, drug/vehicle treatment, 6 days, and 28 days post drug administration. Animals were either given a subcutaneous (S.C.) injection of vehicle (1 ml/kg) or an equivalent volume of psilocin (2 mg/kg). Photometry trace plots were generated showing change in fluorescence as a function of baseline (ΔF/F) and the peak point (PP) and area under the curve (AUC) of the mean signal trace following the air puff administration were used to quantify differences in magnitude and response duration. A two-way mixed effects ANOVA found a main effect of treatment for both PP ($F(3, 51) = 4.067$, $p=0.01$) and AUC ($F(3, 51) = 3.975$, $p=0.01$). Dunnett post-hoc analysis found a significant increase in CeA response duration (AUC) while on psilocin ($p=0.04$) and decrease in CeA response magnitude (PP) four weeks after psilocin administration ($p=0.007$) compared to baseline, with no changes found in the vehicle group. This experiment is currently being repeated in a male only cohort to probe potential sex differences. These data provide rationale for further circuit-based exploration of the effects of psilocin on central amygdala reactivity to an aversive stimulus.

M15. Role of Gabaergic Inhibitory Interneurons in the Emergence of V1 Visual Sensory Processing

Manal Salmi, Ehsan Sabri, Renata Batista_Brito*

Sensory perception not only allows us to receive and integrate information from environment, but also serve as a springboard to initiate behavior adapted to this environment. Growing evidence reports that inadequate sensory (visual) perception could lead to major social interaction disorders or worse, reality distortion, in autistic or schizophrenic patients. The mammalian cerebral cortex is made up of billions of neurons among which excitatory projection neurons are representing 80% of all cortical neurons and GABAergic inhibitory interneurons (INs) 10-20%. Understanding how neurons assemble into circuits that encode inputs, representations, behavioral states is still poorly understood and is likely to provide insight not only into how these circuits function, but also how they malfunction in various neurological conditions. Numerous studies have reported the essential contribution of GABAergic INs at different neocortical development steps and their dysfunction in major neuropsychiatric disorders. However, their contribution in vivo to sculpt the early postnatal neocortical network activity remains largely unknown. Here, we disrupt Parvalbumin (PV) interneurons (main GABAergic INs class), during neonatal development by selectively removing the gene Mef2c from PV-INs and record in vivo how that impacts the early postnatal network activity in V1. These preliminary experiments report that Mef2c is critical for the early activity of PV-INs during neocortical development and as consequences critical for the proper development and maturation of the emergent sensory visual processing in V1.

M16. Sex and Age-Based Differences in Tactile Function Loss in Persons with Type 2 Diabetes

Stacey Gorniak, Patrick Dougherty*

Importance: Recent evidence of sex-based differences in the presentation of Type II Diabetes Mellitus (DM) and its complications has been found in humans, which may directly contribute to sex-based differences in reduced functionality and quality of life in persons with DM (PwDM). Some functionality, such as tactile function of the hands, has significant direct impact on quality of life. Understanding the potential (non-)modifiable bases for the observed variability in tactile function has important implications for both clinicians and PwDM.

Research Design and Methods: A case-control single time point observational study from 2012 – 2020 in an ethnically diverse population-based community setting. The sample consists of 132 adult individuals: 70 independent community-dwelling persons with DM and 62 age- and sex-matched controls (42 males and 90 females in total). The Semmes-Weinstein monofilament test was used to evaluate tactile sensation of the hands.

Results: Tactile sensation thresholds were adversely impacted by sex, age, handedness, poor blood sugar control, and diagnosis of DM and peripheral neuropathy, such that strongly right-handed older adult males with poorly controlled DM and neuropathy possessed the poorest tactile discrimination thresholds. When self-identified minority status was included in secondary analysis, DM diagnosis was no longer significant; however, negative impacts of age, neuropathy, handedness, and poor blood sugar control remained significant.

Conclusion: The data indicate significant impacts of male sex, age, handedness/laterality, self-identified minority status, and metabolic health on the development of poor tactile sensation. This combination of modifiable and non-modifiable factors are important considerations in the monitoring and treatment of DM complications.

M17. Mice Rapidly Update Timed Behaviors in a Serial Fixed Interval Task

Nada Aggadi, Rochelle van der Merwe, Ruth Albert-Lyons, Olivia Lu, Golara Malaki, Charlie Maddox, Marwan Ghanem, Jojo Scott, Caroline Morehouse, Patrick Simen, Christopher Howard*

Temporal perception and timed behavior are essential for survival, though how brain circuits encode time estimates remains mysterious. Much research has investigated how animals time fixed interval durations. Less has investigated how animals learn to update behavior to encode new time intervals, and very little is known about brain circuits contributing to this process. The aim of this study is to investigate whether mice can rapidly update responding in a serial Fixed Interval (sFI) task. In this task, mice are rewarded for lever presses made after a fixed duration ranging from 12 to 60 seconds. This fixed interval is updated after a randomly chosen number of trials (ranging from 13-21 trials). We used three metrics to study temporal updating of timed behaviors: 1. the time when mice first press the lever in each trial, 2. the time of the first bout of presses in each trial (3 presses, each separated by <0.5 sec), and 3. the time when mice reach 63% of their maximum press rate in each trial. We found that mice are capable of rapidly updating

their responding in new blocks, and the average time of first press, time of first bout, and time reaching 63% maximum press rate are all linearly related to fixed interval duration. This updating is often rapid and can take place in only a few trials after the start of a new block. Now, pilot studies are underway to determine how manipulation of secondary motor cortex (M2) using optogenetics in GAD-Cre and CAMKII-Cre mice modifies the speed of updating in this task, and the performance within fixed interval blocks. Our findings provide a platform for investigating the updating of temporal behavioral patterns in a dynamic timing task and will provide new insights into brain circuits involved in this process.

M18. Cholinergic Transmission in the Nucleus Accumbens Core Alters the Flexibility of Sign-Tracking Responses

Erica Townsend, Kenneth Amaya, Elizabeth Smedley, Kyle Smith*

Reward predictive cues can acquire their own motivational value. The physical manifestation of this motivation is often cue-triggered Pavlovian conditioned approach, commonly referred to as sign-tracking. In dynamic environments, inflexible responding to reward cues may become detrimental, suggesting that behavior should be sensitive to these environmental changes and flexibly adjust. Indeed, sign-tracking has been previously shown to flexibly change after introduction of an omission schedule, where deflection of a lever-cue cancels delivery of the reward (Chang and Smith, 2016). However, neural mechanisms underlying this flexibility remain elusive. One area of intrigue is the nucleus accumbens core (NAc), whose role in governing sign-tracking behavior has been extensively studied. Within the NAc, there is a small population of modulatory cholinergic interneurons that have historically received little attention. Recently, these cells have been studied with respect to other flexible behaviors like Pavlovian-to-instrumental transfer. But it is unknown what role cholinergic transmission plays in the regulation of sign-tracking behavior during the omission schedule. To address this, I evaluated the role of local cholinergic transmission in the NAc during an omission schedule following sign-tracking training. Using pharmacological manipulations in rats trained to sign-track, nicotinic receptors in NAc were inhibited during the first five days of the omission schedule following training. In the absence of activity at these receptors, the rats' ability to flexibly alter their sign tracking responses to meet the contingency change was suppressed in comparison to controls; although nicotinic inhibition did not entirely prevent the rats from acquiring the new sign tracking responses. Altogether, these results indicate that activity at NAc nicotinic receptors may contribute to an animal's ability to use new information about cues to flexibly and quickly adjust learned behavioral responses.

M19. Habit Prone Mice Exhibit Compulsive-Like behavior: Potential Involvement of Orbitofrontal MC4R

Sophie Yount, Aylet Allen, Shannon Gourley*

Altering familiar actions based on changes in the surrounding environment is part of everyday life. Goal-directed behavior (i.e., making a choice based on changes in outcome expectation) is antithetical to habitual behavior, which is instead triggered by cues and not outcome predictability. Habitual behavior is adaptive under many circumstances, but it could be antecedent to compulsions – intrusive thoughts that drive persistent and potentially maladaptive behavior. A hallmark characteristic of patients with obsessive

compulsive disorder is hyperactivity of the orbitofrontal cortex (OFC), and melanocortin 4 receptor (MC4R) signaling may be involved. We hypothesized that mice with a natural propensity for habitual behavior would exhibit compulsive-like behavior. We selectively bred mice that defer to familiar behavioral sequences instead of updating instrumental behaviors when expected rewards are not delivered. Their offspring developed the same habitual response bias and compulsive-like and risk-taking behavior. Compulsive-like behavior was corrected by fluoxetine and correlated with instrumental response strategies. We next hypothesized that compulsive-like behavior may be attributable MC4R systems in the OFC. Repeated, but not acute, chemogenetic stimulation of MC4R+ glutamatergic OFC neurons triggered compulsive-like grooming. A prominent theory of addiction and compulsive disorders is that they involve a loss of control over habits. Understanding whether action strategies correlate with compulsions, and whether melanocortin signaling alters cortico-striatal connectivity, will advance future efforts to mitigate harmful habitual behavior.

M20. Investigating the Effect of Differential Striatal Dopamine Projections on Reversal Learning and Immediate Early Gene (IEG) Expression

Rochelle van der Merwe, Marwan Ghanem, Jacob Nadel, Della Copes-Finke, Sean Pawelko, Jojo Scott, Mia Fox, Caroline Morehouse, Robert McLaughlin, Charlie Maddox, Golara Malaki, Christopher Howard*

Behavioral flexibility is key to survival in a dynamic environment. One form of flexibility is reversal learning, or the ability to switch between opposing actions following a change in outcomes. Key to this process is the striatum, a subcortical structure tasked with action selection and learning novel motor behaviors. Early development of motor behaviors is dependent on dorsomedial striatum (DMS), and later becomes dependent on dorsolateral striatum (DLS) as behaviors become inflexible. Similarly, dopamine release in striatum mirrors this medial-to-lateral transition, suggesting lateral dopamine release may be a key mechanism in establishing inflexible behaviors late in learning, though less work has focused on the specific contributions of DMS and DLS dopamine to reversal learning. To investigate how dopamine release in medial and lateral striatum modifies reversal, we trained DATcre X Ai32 mice that selectively express channelrhodopsin-2 in dopamine neurons to perform an intracranial self-stimulation reversal task. We found that selectively stimulating dopamine terminals in DLS renders mice inflexible following reversal of the active lever, while stimulating DMS results in more flexibility. To explore circuit changes in medial and lateral striatum during reversal, we then trained WT mice on a reversal task for food rewards and found that markers of neural activity and synaptic plasticity (c-Fos and Arc, respectively) are more robust in DLS across learning and reversal, while expression in DMS decreases. This supports a model of learning as initially dependent on both DMS and DLS, but diminishing dependence on DMS late in learning. Finally, to explore how DMS and DLS dopamine contribute to reversal for natural reinforcers, we trained mice to press a lever for sucrose pellets and optogenetically drove dopamine release in DMS or DLS during acquisition, before switching the active lever. Preliminary results suggest stimulation of DMS and DLS drive a similar rate of reversal, but DLS mice take slightly longer to fully reverse preference to the newly active lever. This work contributes to our general understanding of how dopamine modifies striatal subcircuits to

switch between different behavioral strategies, and may provide insight into how drugs of abuse promote maladaptive behaviors in drug addiction.

M21. Transcriptional and Anatomical Diversity of Medium Spiny Neurons in the Primate Striatum

Jing He, Michael Kleyman, Jianjiao Chen, Aydin Alikaya, Kathryn Rothenhoefer, Bilge Ozturk, Morgan Wirthlin, Andreea Bostan, Kenneth Fish, Leah Byrne, Andreas Pfenning, William Stauffer*

Medium spiny neurons (MSNs) constitute the vast majority of striatal neurons and the principal interface between dopamine reward signals and functionally diverse cortico-basal ganglia circuits. Information processing in these circuits is dependent on distinct MSN types – cell types that are traditionally defined according to their projection targets or dopamine receptor expression. Single cell transcriptional studies have revealed greater MSN heterogeneity than predicted by traditional circuit models, but the transcriptional landscape in the primate striatum remains unknown. Here, we set out to establish molecular definitions for MSN subtypes in Rhesus monkeys, and to explore the relationships between transcriptionally defined subtypes and anatomical subdivisions of the striatum. Our results suggest at least nine MSN subtypes, including dorsal striatum subtypes associated with striosome and matrix compartments, ventral striatum subtypes associated with the nucleus accumbens shell and olfactory tubercle, and an MSN-like cell type restricted to mu-opioid receptor rich islands in the ventral striatum. Although each subtype was demarcated by discontinuities in gene expression, continuous variation within subtypes defined gradients corresponding to anatomical locations and, potentially, functional specializations. These results lay the foundation for achieving cell-type-specific transgenesis in the primate striatum and provide a blueprint for investigating circuit specific information processing.

M22. Early Life Adversity Diminishes Reward Sensitivity and Slows Reinforcement Learning in Mice

Meghan Gallo, Arif Hamid, Alana Jaskir, Tracy Pan, Dayshalis Ofray, Michael Frank, Christopher Moore, Kevin Bath*

Exposure to early life adversity (ELA) is associated with heightened risk for the development of anhedonia, depression and substance use disorder. Adverse outcomes may reflect ELA-linked impacts on reward pursuit including blunted reward sensitivity, slower reward learning and alterations in reward-related neural activities. However, the effects of ELA on the development of reward motivated behavior and their neural underpinnings remain poorly understood. Here, in a probabilistic bandit task, we use a mouse model of ELA to study sensitivity to reward contingencies and rates of adaptation to changing contingencies across reward rich and reward poor environments. Overall, ELA diminishes reward sensitivity and disrupts reward-related learning and action selection. Importantly, we found evidence that mice exposed to ELA showed slower adaptation when contingencies changed and deficits in sensitivity to reward contingencies as a function of environmental richness. Ongoing work will explore the link between these outcomes and striatal dopamine function as well as computational modeling of behavior.

M23. Association of Subcortical Grey-Matter Volumes with Life-Course-Persistent Antisocial Behavior in a Population-Representative Longitudinal Birth Cohort

Christina Carlisi, Terrie Moffitt, Annchen Knodt, Honalee Harrington, Stephanie Langevin, David Ireland, Tracy Melzer, Richie Poulton, Sandhya Ramrakha, Avshalom Caspi, Ahmad Hariri, Essi Viding*

Neuropsychological evidence supports the Developmental Taxonomy Theory of Antisocial Behavior, suggesting that abnormal brain development distinguishes life-course-persistent from adolescence-limited antisocial behavior. Recent neuroimaging work confirmed that prospectively-measured life-course-persistent antisocial behavior is associated with differences in cortical brain structure. Whether this extends to subcortical brain structures remains uninvestigated.

This study compared subcortical grey-matter volumes between 672 members of the Dunedin Study previously defined as exhibiting life-course-persistent, adolescence-limited or low-level antisocial behavior based on repeated assessments from ages 7-26. Grey-matter volumes of 10 subcortical structures were compared across groups.

The life-course-persistent group had lower volume of amygdala, brain stem, cerebellum, hippocampus, pallidum, thalamus, and ventral diencephalon compared to the low-antisocial group. Differences between life-course-persistent and adolescence-limited individuals were comparable in effect-size to differences between life-course persistent and low-antisocial individuals, but were not statistically significant due to less statistical power. Grey-matter volumes in adolescence-limited individuals were near the norm in this population-representative cohort and similar to volumes in low-antisocial individuals.

Although this study cannot establish causal links between brain volume and antisocial behavior, it constitutes new biological evidence that all people with antisocial behavior are not the same, supporting a need for greater developmental and diagnostic precision in clinical, forensic, and policy-based interventions.

M24. Conformation-Sensitive Antibodies to Protein Kinase C to Study Opioid Receptor Signaling

Achla Gupta, Mariana Lemos-Duarte, Ivone Gomes, Lakshmi Devi*

Antibodies are powerful tools to explore signal transduction pathways. We developed an integrated approach that uses yeast display antibody libraries from the B cells of immunized rabbits in combination with high-throughput microscopy/machine learning pipeline, to identify and validate 137 recombinant high affinity antibodies against understudied synaptic proteins. Here we report findings from studies using a conformation-sensitive antibody, named C2-CAT-cPKC, to examine the dynamics of PKC activation by opioid receptors. The C2-CAT-cPKC antibody recognizes a region of PKC that is exposed upon kinase activation, and hence can be used to readily detect and quantify the level of 'active' endogenous PKC in native cells and tissues; this antibody works well in a variety of assays (immunofluorescence, immunohistochemistry, and ELISA). Using this antibody we investigated the dynamics of opioid receptor-mediated activation of PKC in cells expressing mu opioid receptors; a comparison of temporal

dynamics of activation was made between endogenous opioid peptides and exogenous ligands (opioid alkaloids, opiates and synthetic ligands). We find substantial differences between ligands; whereas some ligands cause a rapid and transient increase, others cause a slow and sustained increase in the level of active PKC illuminating ligand-dependent differential activation of opioid receptors. Finally, acute administration of morphine was found to lead to significant increases in active PKC levels in the ventrolateral periaqueductal gray region and the magnitude of this increase is reduced upon chronic morphine administration. Together, we describe the generation of a novel tool to study opioid receptor signaling that provides insights into the dynamics of PKC-mediated activation in response to different opioid peptides and opioids.

M25. Inhibitory Co-Transmission from Midbrain Dopamine Neurons Depends on Presynaptic GABA Reuptake

*Riccardo Melani, Nicolas Tritsch**

Dopamine (DA)-releasing neurons in the substantia nigra pars compacta (SNc) inhibit target cells in the striatum through postsynaptic activation of gamma-aminobutyric acid (GABA) receptors. However, the molecular mechanisms responsible for GABAergic signaling remain unclear, as SNc DA neurons lack the classical GABA synthetic enzymes Gad65 and Gad67, as well as the vesicular GABA transporter Vgat. Here we show that aldehyde dehydrogenase 1a1 (Aldh1a1), an enzyme proposed to substitute for Gad65/67 in SNc DA neurons is neither necessary nor sufficient for GABAergic co-transmission from these cells. Instead, we demonstrate that SNc DA neurons obtain GABA exclusively through presynaptic uptake using the membrane GABA transporter Gat1 (encoded by Slc6a1), which they package for vesicular release using the vesicular monoamine transporter Vmat2. Our data therefore show that presynaptic transmitter recycling can substitute for de novo synthesis and expand the range of molecular mechanisms available to neurons to support synaptic communication.

M26. An Engineered 3D In Vitro Model of Glial-Mediated Neuroinflammation: Toward Understanding Multicellular Mechanisms Underlying Neurodegenerative Diseases

Sophie Brown, Elaina Atherton, David Borton*

Neuroinflammation is widely recognized as having a deleterious role in the pathogenesis and progression of many neurodegenerative diseases and is characterized by complex multicellular processes driven by innate immune mechanisms. However, the specific role of glial cell activation and the subsequent influence on the structure and function of neuronal networks remains unclear. As such, there is a growing need for an efficient model system that can sufficiently delineate the causal and correlative roles of glial cells in the neuroinflammatory processes that perpetuate neuronal network dysfunction in disease. Three-dimensional (3D) primary neural cell culture models offer a unique opportunity to study the complex multicellular dynamics of neuroinflammation underlying disease. These engineered and well-controlled models provide the operational benefits of in vitro tools while preserving many features of the in vivo microenvironment including, but not limited to, the formation of a self-assembled extracellular matrix and inter-cellular inflammatory signaling. Here, we demonstrate the utility of such a model for investigating the effects of glial-mediated neuroinflammation on neural network dynamics through live longitudinal functional calcium imaging of microtissues after acute exposure to lipopolysaccharide (LPS). Graph theory analysis of microcircuit activity revealed significant increases in functional connectivity and disrupted community structure following LPS exposure. Additionally, we explored the advantage of cell-specific manipulation within the in vitro neural microenvironment through depletion of microglia cells in combination with functional imaging to further characterize microglia-specific roles in the neuroinflammatory mechanisms that lead to dysregulation in neural network dynamics. These experimental methodologies provide powerful tools for investigating the underlying mechanisms of microglia in neuroinflammatory and neurodegenerative disease states.

M27. Testing the Brain Maintenance and Cognitive Reserve Hypothesis of Cognitive Aging: Application to Vascular and Metabolic Risk Factors

Bryan Neth, Timothy Lesnick, Anna Castillo, Scott Przybelski, Jonathan Graff-Radford, Mary Machulda, Michelle Mielke, Ronald Petersen, Val Lowe, Clifford Jack Jr., David Knopman, Prashanthi Vemuri*

Background: Two pathways that help explain cognitive health include 1) brain maintenance – referring to the relative absence of brain pathology over time; 2) cognitive reserve – a property of the brain that allows for sustained cognitive ability in the presence of brain pathology. Both pathways influence cognitive aging and are best understood using longitudinal data. Our goal was to assess the effect of modifiable vascular/metabolic and lifestyle enrichment factors on these pathways using longitudinal brain changes measured on structural magnetic resonance imaging (MRI) and longitudinal cognitive decline. Lastly, we combined these pathways and their relationships in the same model.
Methods: We identified 1250 participants from a well-characterized sample of older adults from the Mayo Clinic Study of Aging with both longitudinal MRI and cognitive data.

Linear mixed models were performed to assess the impact of modifiable factors on brain maintenance and cognitive reserve. Latent growth curve models were used to assess the impact of brain maintenance and cognitive reserve on longitudinal cognition.

Results: The mean age of our sample was 78.8 years, with 45.4% female and 27.1% APOE4 carriers. Mean follow-up time was 4 years with a mean of 3.2 MRI scans per participant. Poorer vascular/metabolic health (presence of vascular/metabolic conditions) was associated with lower temporal region cortical thickness ($p<0.001$) and lower global cognition ($p=0.002$). Higher baseline cognitive reserve as assessed by education/occupation composite ($p<0.001$) and late-life cognitive activities ($p<0.001$) were associated with higher global cognition. Conversely, late-life physical activities were related to lower global cognition ($p=0.008$). Our final latent growth curve SEM fit the data well. Figure 1 displays output from latent growth curve models (summarized in Table 1).

Conclusions: We found that brain maintenance and cognitive reserve pathways were related to better cognition over time. We further showed that vascular/metabolic health impacts long-term cognitive outcomes (i.e. cognitive aging) primarily through the brain maintenance pathway. These data provide a modeling scheme for future studies and can aid in assessing the pathways by which individual factors may influence cognitive aging.

M28. Tau Interactome and Functional Study of AKAP9 I2558M Mutation, Alzheimer's Associated Risk Gene Mutation in African American Cohort

Samuel Hersh, Yang You, Roshanak Aslebagh, Scott Shaffer, Seiko Ikezu, Jesse Mez, Kathryn Lunetta, Mark Logue, Lindsey Farrer, Tsuneya Ikezu*

Alzheimer's disease (AD) is a neurodegenerative disease that is the most common cause for dementia. African Americans (AAs) are a group of people with high prevalence of AD containing different genetic risk factors than non-Hispanic Caucasian. A rare allele (rs144662445) in the A kinase anchoring protein 9 (AKAP9) loci is genetically associated with AA AD cases, although its pathogenic implication is unknown. The purpose of this study is to investigate the impact of the AKAP9 rs144662445 mutation in SH-SY5Y human neuronal cells expressing P301L mutant tau, which was introduced by CRISPR-Cas9 engineering. We observed a significant increase of tau phosphorylation at the Ser396/Ser404 site in both immunocytochemistry and ELISA. Furthermore, examination of the tau interactome via affinity purification of total tau followed by quantitative mass-spectrometry revealed differentially expressed tau-interacting proteins in AKAP9 mutant cells, which are enriched in biological pathways for oxidative activity, protein translation, and RNA localization. These results were validated by further functional studies showing that AKAP9 mutant SH-SY5Y cells have increased oxidative stress and reduced protein synthesis as compared to AKAP9 WT SH-SY5Y cells, which are indicative of neurotoxic changes by AKAP9 mutation. Our results demonstrated specific functional effects of the rs14462445 mutation of AKAP9 on accumulation of phosphorylated tau and neurotoxic changes, which may have relevance to the higher prevalence of AD in AA cohorts.

M29. Local Synthesis of Estrogen in the Ventral Striatum's Tubular Striatum Regulates the Appetitive Nature of Stimuli

Katherine Wright, Natalie Johnson, Jamie Wilson, Daniel Wesson*

17β-estradiol (E2), largely synthesized in the periphery, is a potent regulator of cognition, memory, and motivated behavior. Likewise, brain-derived E2 confers rapid effects on neural activity which has implications for its influence on in-the-moment responses to environmental cues, including those predicting reward availability. The tubular striatum (TuS, also known as the olfactory tubercle) is a ventral striatum subregion that plays an important role in motivated behavior and the reinforcing effects of cocaine and natural rewards. The TuS has ample expression of aromatase, the enzyme responsible for E2 synthesis, and the TuS is necessary for attraction to innately rewarding stimuli including odors. Therefore, we reasoned that TuS E2 is important for mediating attraction to stimuli. To test this, we gonadectomized male and female adult C57bl/6j mice to eliminate influence of peripheral sex steroid hormones, and later infused the aromatase inhibitor letrozole bilaterally into the TuS. We took advantage of odors that possess innate salience, including social odors from gonadally-intact male and female mice, as well as monomolecular odorants with no intrinsic hedonic value, and we presented them to mice and used unrestrained whole-body plethysmography to monitor odor detection, discrimination, learning, and importantly, arousal-elicited sniffing over repeated trials. All mice displayed intact abilities to detect odors, as well as intact capabilities to discriminate between different odors and to habituate to them after repeated presentations. This indicates that TuS E2 is not necessary for basic odor perception. Interestingly, inhibition of E2 synthesis in the TuS of females, but not males, increased interaction with female social odors that was sustained across multiple presentations, indicating an enhanced attraction to this stimulus in females. Importantly, these results were not due to basal respiratory levels, as all mice had similar baseline respiratory profiles. These results indicate that biological sex and local E2 in the TuS interact to influence the appetitive nature of social cues. This work points to an important role for E2 in the TuS to influence motivated behavior and has implications for the brain functions that underlie substance use disorders.

M30. Effects of Anesthesia and Oxytocin on Dopamine Signaling in the Rat Dorsal Striatum

David Daberkow, Darren Ginder, Mitchell Gainer*

Oxytocin (OXT) is involved in many aspects of brain function. Current research suggests that, due to the possible modulatory effect of OXT on learning and memory circuitry, OXT treatment for depression and addiction could be beneficial. Defining the neural mechanisms of OXT is crucial to understanding how OXT may be therapeutic for certain psychological disorders. Dopamine (DA), a neurotransmitter highly implicated in learning and memory, may be modulated by OXT. In general, OXT and DA receptors are located within the same brain regions. More specifically, there is overlap in the expression of OXT and DA receptors in the dorsal and ventral striatum. Furthermore, OXT fibers innervate DA neurons. The neuroanatomical association between the dopaminergic and oxytonergic systems provides a neurological mechanism by which OXT could potentially alter DA neurotransmission. Male Sprague-Dawley rats were anesthetized, immobilized in a stereotaxic frame, skin/fascia was cleared, and small holes drilled in the skull for

placement of electrodes. A reference electrode (Ag/AgCl) was placed just below dura and a fast-scan cyclic voltammetry electrode was placed in the dorsal striatum (+1.0 AP, +2.0 ML, -5.0 DV). Subsequently, a stimulating electrode was placed just above the medial forebrain bundle (-4.6 AP, +1.4 ML, -7.0 DV). Constant current, biphasic stimulus pulses (60 Hz, 60 pulses, 300 µA) were applied and the stimulating electrode was incrementally lowered until a robust DA signal was evoked. Once clear and consistent DA signals were observed, intranasal OXT (1.0 µg/kg or an equivalent volume of saline for controls) was administered. Intranasal OXT increased DA release in the dorsal striatum, relative to controls (saline-treated rats). These results suggest OXT modulates DA neurotransmission and is potentially therapeutic for psychological disorders.

M31. Repetitive Mild Traumatic Brain Injuries Increase Motor Impulsivity but Not Choice Impulsivity and Cause Minor Changes in Glial Pathology in Male Rats

Sarah Wampler, Cole Vonder Haar, Kris Martens*

Mild traumatic brain injuries (mTBIs) account for about 90% of all brain injuries, but despite being mild, can result in enduring behavioral impairments. The purpose of these studies was to investigate whether repeated closed head injuries would generate behavioral deficits or changes in glial pathology. Rats were trained on the 5-choice serial reaction time task (5CSRTT), a measure of attention and motor impulsivity (Experiment 1 and 2), and the delay discounting task (DDT), a measure of choice and motor impulsivity (experiment 2 only). Once responding stabilized, injuries were administered using the Closed-Head Impact Model of Engineered Rotational Acceleration (CHIMERA) with either a rubber tip (experiment 1a) or a metal tip (experiment 1b and 2). Rats were injured once a week, twice a week, or given a sham injury for 4 weeks (Experiment 1a), 3 weeks (experiment 1b), and 5 weeks (experiment 2) with behavior tested daily each week. Immunohistochemistry stains were performed to assess ventricle size, microglia activation, and astrocyte activity. Rats injured with a rubber tip had no impairment in behavior while rats injured with a metal tip had heterogenous behavioral deficits on the 5CSRTT and the DDT. Changes in glial pathology were small and differed between the experiments. These data suggest that behavioral deficits can occur following repeated mTBIs without major changes in pathology. It is important to continue investigating the pathological and behavioral effects of mTBIs to better understand the human condition.

M32. Plasticity of Perisynaptic Astroglia During Ischemia-Induced Spreading Depolarization

Sergei Kirov, Jeremy Sword, Ioulia Fomitcheva*

Spreading depolarization (SD) that occurs during stroke is a mechanism of abrupt, massive ion translocation between extracellular and intracellular space resulting in a net gain of excess electrolytes in the cytoplasm and onset of cytotoxic edema. High astroglial capacity for glutamate clearance and K+ buffering aids in the recovery of SD-evoked disturbance of ion homeostasis. Since perisynaptic astroglial processes are beyond the resolution of the 2-photon microscopy, nothing is known about the impact of SD on the ultrastructure of a tripartite synapse. We used quantitative serial section electron microscopy (ssEM) to study

astroglial processes at the axon-spine interface (ASI) during a single SD and recovery. SD was evoked by a transient bilateral common carotid artery occlusion (BCCAO) in urethane-anesthetized male and female mice. The DC potential and in vivo 2-photon, laser speckle, and intrinsic optical signal imaging were used to monitor onset and recovery from SD. Mice in the Sham group were perfusion-fixed through the heart with mixed aldehydes after baseline imaging and before BCCAO. Mice in the SD group were perfusion-fixed after 4.4±0.2 min of SD onset. In the Recovery group, blood reperfusion was started at 10–15 s after the onset of SD, and mice were perfusion-fixed at 70±3.5 min of blood reperfusion. Overall, 480 synapses (160 per group) were randomly selected and analyzed in 3D blind to the conditions. We have shown that astroglial mitochondria are remarkably resilient to a short-lasting SD. Our findings reveal that perisynaptic astroglial processes are present at the ASI during SD and after recovery. We found an increase in perisynaptic astroglial ensheathment at larger synapses suggesting that as these synapses release more neurotransmitter during SD, they attract astroglial processes to a discrete portion of their perimeters, further enhancing astrocytic ability to protect fine synaptic circuitry in stroke. Supported by NIH RO1NS083858 (SAK)

M33. The Effect of Mild Traumatic Brain Injury on Orexin Neuron Function

Rebecca Somach, Ian Jean, Akiva Cohen*

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. An increased number of patients are living with the sequelae of mTBI each year. Sleep disorders are a common consequence post mTBI that lead to negative disruptions in daily life. The cause of these injury induced sleep disorders is not currently understood. Changes to sleep circuitry are known to cause sleep disorders, but changes in sleep circuitry due to mTBI are understudied. A component of sleep circuitry that is a candidate for alterations after injury are orexin neurons. These neurons produce orexin, a neuropeptide responsible for arousal and wakefulness. Following mTBI, studies in rodents have shown an increase in sleepiness and a decrease in orexin neuropeptide in the brain, indicating damage to orexin neurons. However, previous work from our lab has shown that the number of orexin neurons is not decreased after injury. This indicates that reduced orexin production after mTBI is not due to cell death of orexin neurons. This led us to the hypothesis that the physiological function of orexin neurons is altered after mild traumatic brain injury. To test this hypothesis, our lab used the lateral fluid percussion injury (LFPI) method to induce mTBI in mice 6-8 weeks of age. To locate the orexin neurons, we used a transgenic mouse model wherein orexin neurons express EGFP. With this genetic marker, the whole cell patch clamp technique was used to record electrophysiological activity in these neurons. Conventional current clamp recordings were conducted to measure intrinsic excitability parameters i.e., action potential properties and passive cell properties. Whole cell voltage clamp recordings were employed to determine changes to afferent synaptic activity onto orexin neurons. These techniques can elucidate the effects that mTBI has on the physiological properties of orexin neurons and characterize changes that injury induces in neuronal sleep circuitry.

M34. Interactions Between Ceftriaxone and Voluntary Abstinence on Relapse to Cocaine Seeking

Yasmin Padovan-Hernandez, Giselle Rojas, Lizhen Wu, Lori Knackstedt*

Cocaine use disorder is characterized by high rates of relapse even after long periods of abstinence and poses significant threats to personal and societal well-being. Contingency management is currently the most effective behavioral treatment for most addicts, offering non-drug rewards to maintain abstinence, however, most addicts relapse once treatment is discontinued. While choice-based voluntary abstinence provides a translationally relevant rodent model of recovery from addiction, it hasn't been utilized in a cocaine self-administration model yet. Here, we trained male and female Sprague-Dawley rats to self-administer sucrose pellets (6-10 days, 2hr/day). Once acquisition criteria were met, rats self-administered intravenous cocaine (12 days of 10 or more infusions, 2 hr/day). Rats were then assigned to undergo either voluntary or forced abstinence for 14 days. Voluntary abstinence entailed operant sessions with both sucrose- and drug-associated cues and the opportunity to choose between the two rewards. Rats assigned to forced abstinence were handled daily but did not go back to the operant environment. On Day 15, a relapse test was conducted; only the drug-paired lever and inactive lever were available. To test the additive efficacy of behavioral and pharmacological treatments in relapse prevention, rats received either ceftriaxone (200 mg/kg) or vehicle (saline) injections during the last seven days of abstinence. Ceftriaxone is a beta-lactam antibiotic that has previously been shown to attenuate relapse to drug-seeking behaviors in rodents. Rats were perfused immediately after the relapse test for the quantification of Fos protein expression, allowing us to compare expression between groups and assess effects of both abstinence type and ceftriaxone on the circuitry underlying relapse to cocaine-seeking. Together, our results confirm the engagement of differing circuitry underlying relapse following voluntary abstinence and suggest that, in this model, reward type (sucrose pellet vs palatable food pellet) highly impacts voluntary abstinence behavior. Additionally, ceftriaxone failed to attenuate relapse in animals undergoing voluntary abstinence, suggesting its ability to decrease cocaine-seeking is dependent on neurobiological changes following complete drug abstinence.

M35. Accelerated Theta Burst Stimulation for Bipolar I and II: Assessing Clinical Changes Pre- and Post-Treatment

Kristin Raj, Nolan Williams*

Accelerated intermittent theta-burst stimulation (aiTBS) is a novel, rapid-acting form of repetitive transcranial magnetic stimulation (rTMS) that has shown promise in rapidly treating highly treatment-refractory patients with major depressive disorder (MDD). In this case series, we applied aiTBS to a pilot sample of bipolar I and II patients and observed similar results of our previous work showing a dramatic reduction in depressive symptoms. In this sample (n=8), we observed all participants to have experienced symptomatic remission at some point in the 4-week follow-up. No serious adverse events were observed. Interestingly, 3 of the bipolar patients reach HDRS6's criteria for remission after just one day of treatment. These results encourage future investigation into the optimization of the stimulation parameters and dosage for bipolar patients using closed-loop, concurrent EEG recordings.

M36. Unraveling the Mechanisms Tying the Gut Microbiome to Central Nervous System Diseases

*Stephen Skolnick**

The human gut microbiome has emerged as a major mediator of health and disease in multiple domains, including neuropsychiatry. Recent work in both humans and animals has demonstrated that microbiome modulation is a promising therapeutic avenue in CNS disorders which are inadequately managed by current standards of care. However, identifying the mechanisms which underlie the therapeutic effects of microbiome modification is a daunting task that will require new disease models, new technologies, and the integration of metagenomic, metabolomic, epidemiological, and other data. Here, we review recent translational findings on the gut-brain axis, and provide an overview of our process for identifying and characterizing microbes with the capacity to influence mental health.

M37. Dynamics of VTA Dopaminergic Neuronal Activity During Sleep

Bibi Sulaman, Su Wang, Gideon Rothschild, Ada Diane Eban-Rothschild*

Phasic activation of ventral tegmental area dopaminergic (VTA-DA) neurons is critically implicated in many vital processes, including reinforcement learning and motivational regulation. VTA-DA neurons are also highly active during rapid eye movement sleep (REMs) and show little activity during non-rapid eye movement sleep (NREMs). However, the function of dopamine release during sleep, and whether and how VTA-DA activity varies within a day, across days, and following different waking experiences is undetermined. A better understanding of dopamine dynamics during sleep could have large implications for treating disorders that affect both dopaminergic signaling and sleep, including substance abuse and major depression. Here, we aimed to determine the relationships between VTA-DA population dynamics during NREMs and REMs episodes, circadian time and waking experiences at the sub-second resolution. We stereotaxically injected into the VTA of Dat-cre mice (n=10 males and females) an AAV carrying the calcium indicator GCaMP6f/7f and implanted fiber optic probes and EEG/EMG recording electrodes. We simultaneously recorded calcium-dependent fluorescence, EEG/EMG signal and video data under baseline conditions and following aversive and appetitive experiences. We found that VTA-DA population activity during REMs, NREMs and NREMs-to-REMs transitions is strongly modulated by sleep-state relevant EEG bands, on multiple temporal scales. Further analyses address the modulation of these patterns following fear and reward learning. As many neuropsychiatric disorders are associated with sleep disturbances and dopamine dysregulation, our findings provide critical insights that could set the stage for further interrogations into maladaptive alterations in dopamine activity during sleep.

M38. Does TMS Work Through LTP?

Joshua Brown, Shiwen Yuan, DeVries William, George Mark*

The fundamental mechanisms of Repetitive Transcranial Magnetic Stimulation (rTMS) are poorly understood. Insights could improve clinical treatments through targeted navigation of the infinite rTMS parameter space. Evidence for long-term potentiation (LTP) lacks specificity in human studies. Moreover, pharmacology combined with mechanism-revealing paired-pulse (PPTMS) neurophysiology measures before and after rTMS are essentially unexplored.
To test the sufficiency of n-methly-d-aspartate (NMDA) receptor agonism on PPTMS, including intracortical inhibition and facilitation (ICI, ICF), before and after 10-Hz rTMS in ten healthy adults.

Methods: In this double-blind randomized crossover study, ICI and ICF were obtained from a subthreshold conditioning pulse followed by a suprathreshold test pulse at 3 ms and 15 ms apart, respectively. 10 Hz rTMS duty cycle was 1.5s on, 58.5 s off at 80% motor threshold. 100 mg d-cycloserine (DCS) or identical placebo capsule was adminisitered 2 hours before rTMS. Mean ICF percent change for post-rTMS – pre-rTMS with DCS was -0.48, compared to 0.36 with placebo (Figure 1B, $p = 0.037$, Cohen's $d = 1.13$). Mean ICI percent change post-rTMS – pre-rTMS was -0.26 with DCS, compared to 0.25 with placebo (Figure 1D, $p = 0.027$, Cohen's $d = 1.16$).

In conclusion, 10-Hz rTMS in the motor cortex produced facilitation through glutamatergic transmission; and when combined with DCS, appears to occlude ICF, and initiate homeostatic depression unmasked by ICI. These data provide evidence towards an LTP-like mechanism underlying 10-Hz rTMS.

M39. Ultrastructural Analysis of GluD1-Cbln1 Signaling in the Spino-Parabrachio-Amygdaloid Pain Pathway

Diane Choi, Chris Kozuch, Yoland Smith, Shashank Dravid, Ratnamala Uppala*

Chronic pain affects 11-40% of the U.S. population. Besides leading to long-term disability, chronic pain can also result in the development of anxiety, depression, and drug abuse. The spino-parabrachio-amygdaloid pathway is known for integrating nociceptive and emotional-affective processing in chronic pain modulation. Of particular interest is the glutamate-delta 1 (GluD1) – cerebellin 1 (Cbln1) signaling that occurs in the central amygdala. Unlike typical ionotropic glutamate receptors, GluD receptors largely act as synaptogenic regulators. They form a trans-synaptic complex with presynaptic neurexin and Cbln1 to form and maintain synapses. Parabrachial (PB) neurons, which highly express Cbln1, project to the lateral and capsular subdivisions of the central amygdala (CeLC), where GluD1 preferentially localizes with protein kinase C δ, one of the two main cell types in the CeLC. We hypothesized that the GluD1-Cbln1 complex has a significant role in the PB-driven excitation-inhibition balance in the CeLC and that changes in this complex contributes to pain persistence. In this study, we used double-immunolabeling to label calcitonin gene-related peptide (CGRP), which arises exclusively from PB, and GluD1 in both wild-type (WT) and complete Freund's adjuvant (CFA) inflammatory pain model mice brain tissue. We then utilized electron microscopy to reveal colocalization of

GluD1-CGRP in the CeLC. Preliminary data from WT mice demonstrate dense aggregates of GluD1 immunoreactivity at most, but not all, axosomatic symmetric synapses formed by CGRP-containing terminals. Occasionally, CGRP-positive axodendritic synapses were also labeled for GluD1. In addition to this strong subsynaptic expression, a significant amount of GluD1 immunoreactivity was expressed intracellularly and extrasynaptically on dendrites and soma of CeLC neurons. As we continue collecting data, we will determine how altered is the subcellular and subsynaptic pattern of GluD1 expression and how disrupted is the structural morphology of CGRP terminals in the CFA mouse model. A better understanding of GluD1-Cbln1 structural signaling will allow us to not only elucidate the synaptic ultrastructure of this pain pathway, but may also reveal new targets for mitigating chronic pain.

M40. Estrogen and Serotonin Synergistically Enhance the Release of interleukin-6 and Fractalkine From Murine Macrophages: A Potential Mechanism Underlying Sex Differences in Pain

Taylor Hickman, Sukhbir Kaur, Emily Simmons, Laura Hanson, Dayna Averitt*

Sex differences in the immune system could contribute to pain conditions more prevalent in women. In the peripheral nervous system, serotonin (5HT) can be released by immune cells, including macrophages, where it can bind to excitatory 5HT receptors, including 5HT2A, expressed on nociceptors to initiate and sensitize pain signaling. Macrophages reportedly express estrogen receptors and may be sensitive to the gonadal hormone levels in females. We previously reported that 5HT evokes significantly greater pain sensitivity when gonadal hormone levels are in flux and that 17β-estradiol (E2) enhances 5HT's nociceptive effects on sensory neurons. However, it remains unclear if E2 can modulate the release of 5HT or other peripheral proinflammatory mediators from immune cells to contribute to pain. Here we hypothesized that E2 triggers the release of 5HT and/or proinflammatory cytokines and chemokines from cultured male and female murine macrophages. Supernatant from IC-21 (male C57BL/6) or J774A.1 (female BALB/cN) cultures was collected before and after 1-hour treatment with 150 pM, 1 nM, or 50 nM E2 or vehicle and 5HT release was quantified by ELISA. These concentrations were used to mimic the high and low E2 levels observed during diestrus and proestrus of the rat estrous cycle. In separate cultures, supernatant was collected before and after 1-hour treatment with 100 μM 5HT, 50 nM E2, 5HT + E2, or vehicle and the release of cytokines and chemokines were quantified using a Proteome Profiler Cytokine Array. Macrophages were then fixed in 10% formalin and ERα, ERβ, and 5HT2A receptor expression was detected by immunocytochemistry. A separate group of macrophage cultures were treated with 50 nM capsaicin (nociceptive stimulus), 10 μM 5HT + 50 nM capsaicin, 50 nM E2 + capsaicin, or 5HT + E2 + capsaicin and cell lysates were analyzed by Phospho-Kinase Array. We report that proestrus-level E2 triggers release of 5HT from macrophages and E2 + 5HT synergistically increased the release of IL-6 and fractalkine and phosphorylation of p38, JNK, and Src kinases, implicating an intracellular interaction between ERα and 5HT2A. Together, our data suggest that E2 modulates release of proinflammatory mediators from macrophages which is exacerbated by 5HT, providing a novel mechanism underlying sex differences in pain.

TU1. The Effects of Monoamine Releasers and Reuptake Inhibitors on Behavior Maintained by Social Reinforcement

Mark Smith, Jessica Sharp*

Access to a social partner is reinforcing and has positive incentive value in humans and rodents. Monoamine neurotransmitters play important roles in social behavior, but little research has examined their role in social reinforcement. The purpose of this study was to determine how pharmacological manipulations of dopamine, norepinephrine, and serotonin influence the positive reinforcing effects of social contact. To this end, male and female Long-Evans rats were pretreated with acute doses of the selective dopamine reuptake inhibitor, WIN35,428, the selective norepinephrine reuptake inhibitor, atomoxetine, the selective serotonin reuptake inhibitor, fluoxetine, the nonselective monoamine reuptake inhibitor, cocaine, and the nonselective monoamine releasers d-amphetamine and (±)-MDMA. Ten minutes later, the positive reinforcing effects of 30-s access to a same-sex social partner was examined on a progressive ratio schedule of reinforcement. To determine whether the reinforcement-altering effects of these drugs were specific to the social stimulus, the reinforcing effects of a nonsocial stimulus (30-s access to an athletic sock of similar size and coloring as another rat) was determined in control subjects. WIN35,428, amphetamine, and cocaine, but not atomoxetine, fluoxetine, or MDMA, dose-dependently increased breakpoints maintained by a social partner under conditions in which responding maintained by a nonsocial stimulus was not affected. These data indicate that increases in synaptic dopamine, but not synaptic norepinephrine or serotonin, increases the positive reinforcing effects of social contact in both male and female rats.

TU2. The Role of Striatal Enkephalin in Modulation of Cocaine Seeking

Kanako Matsumura, In Bae Choi, Amanda Harmon, Lauren Dobbs*

Dopamine release in the striatum is linked to cocaine's rewarding effects, but the mechanisms downstream of dopamine release driving cocaine seeking are still poorly understood. One potential mechanism is enkephalin, an opioid peptide highly expressed in striatal neurons that is implicated in cocaine reward. Global knockout of Penk, the gene encoding met-enkephalin, is reported to decrease cocaine self-administration; however, it remains unclear whether this effect is driven by striatal enkephalin or another source. Here, we show that enhancing enkephalin tone in the ventral striatum (VS) of wildtype mice during cocaine conditioning trials potentiated acquisition of cocaine place preference (CPP). In addition, repeated cocaine exposure increased striatal Penk mRNA expression regardless of administration route, implicating striatal enkephalin's role in cocaine reward. To address the necessity of striatal enkephalin in cocaine reward, we generated transgenic mice with a targeted deletion of enkephalin from striatal neurons (D2PenkKO). Analysis of Penk mRNA and met-enkephalin peptide expression confirmed a significant reduction of enkephalin within the dorsal and ventral striatum of D2PenkKOs relative to littermate

controls. D2PenkKOs showed attenuated cocaine CPP compared to littermate controls. To determine whether knockdown of enkephalin selectively in the VS is sufficient to block CPP, we injected AAV-Cre into the VS of Penkf/f mice (VSPenkKD). VSPenkKD acquired CPP at a similar level compared to the Penk-EGFP controls, suggesting that VS enkephalin is not necessary for cocaine CPP. Naloxone blocked the expression of CPP in controls, but had no effect in VSPenkKD, suggesting that antagonizing VS enkephalin attenuated cocaine reward. These data indicate that heightened enkephalin tone in the VS potentiates cocaine reward, and striatal enkephalin may be necessary for full expression of conditioned cocaine reward.

TU3. Infralimbic Pyramidal Neuron Activity After an Unreinforced Lever Press is Necessary for Encoding Extinction of Heroin Seeking in Rats

Matthew McGregor, Kelle Nett, Alexa Zimbelman, Ryan Lalumiere*

The medial prefrontal cortex, specifically the infralimbic cortex (IL), is implicated in the regulation of drug-seeking behavior. Our laboratory has shown that activity in the IL following an unreinforced lever press is critical for encoding the extinction of cocaine seeking. For heroin seeking, however, evidence on the role of IL has been mixed. To determine whether IL activity is similarly necessary for extinction of heroin seeking, we employed an activity-controlled optogenetic approach to inhibit IL pyramidal neurons for 20s immediately after unreinforced lever presses during extinction training. Male and female Sprague-Dawley rats received bilateral injections of AAV-CaMKII-eNpHR3.0 into IL and bilateral optical fibers above IL. Rats then underwent 12d of heroin self-administration training, where lever presses produced a heroin infusion, light/tone cues, and lever retraction. Then, rats proceeded with 5d of extinction sessions, where lever presses produced lever retraction and 20s of laser illumination to inhibit IL pyramidal neurons following an unreinforced lever press. This was followed by 7d of unmanipulated extinction sessions, where lever presses resulted only in lever retraction, which served as an index of retention of extinction learning. Preliminary results indicate that inhibiting IL activity after unreinforced lever presses increases lever pressing in male rats during the initial 5d of extinction training, suggesting impaired encoding of extinction learning. Moreover, rats that received inhibition also had impaired retention of extinction learning, as indicated by increased lever pressing during the 7d of unmanipulated extinction sessions. This finding indicates that IL activity in the 20s following an unreinforced lever press is critical for encoding the lever press-no reward contingency that facilitates extinction of heroin seeking, suggesting that IL activity is similarly important for encoding extinction of both cocaine and heroin seeking.

TU4. Compartment-Specific Plasticity in Mesolimbic Dopamine Dynamics Following Contingency Learning

*Suzanne Nolan, Brooke Christensen, Patrick Melugin, Hannah Branthwaite, Zahra Farahbakhsh, Michelle Kwon, Erin Calipari, Cody Siciliano, Kirsty Erickson**

Striatal dopamine release during motivated behaviors has been extensively investigated for

its role in contingency learning. While the behavioral events and task variables that trigger action potentials in midbrain dopamine neurons or downstream dopamine transients have been the subject of extensive investigation, much less is known as to whether experience imparts lasting plasticity of dopamine release sites. Previous work has outlined experience-dependent induction of classical plasticity mechanisms in dopamine-expressing neurons; however, dopamine is released from multiple cellular compartments, including somatodendritic and terminal compartments, via distinct mechanisms, and both somatodendritic and axonal dopamine release are dissociable from action potential activity. Using ex vivo fast-scan cyclic voltammetry (FSCV) and optical slice imaging methods paired with pharmacology, we characterized compartment-specific plasticity at various points across learning. We reveal sex-specific and compartment-specific experience-dependent plasticity in dopamine release mechanisms as an important substrate of reward learning. Our results indicate increased axonal dopamine release in male, but not female, animals following discriminated operant learning, associated with distinct aspects of behavior during the task, while somatodendritic dopamine release appears to be reduced following task learning. Further, we utilized fiber photometry to record in vivo dopamine dynamics in both the terminal and somatodendritic compartments, revealing compartment-specific activity signatures across contingency learning, suggestive of a regulatory role for somatodendritic dopamine release across the task. Overall, the results of these experiments support temporally- and compartment-specific roles of dopamine in basal cognitive functions, with broad implications regarding the critical nature of dopamine plasticity in specific learning events and ultimately further extend our understanding of these processes in both health and disease.

TU5. Naltrexone Reduces Opioid Choice and Relapse in a Heroin Choosing Subpopulation

Victoria Chang, Jamie Peters*

We recently established a preclinical model of heroin addiction designed to measure the propensity to choose opioids over natural rewards, a hallmark of opioid addiction. This model yields subpopulations of rats that prefer heroin versus food, with a population average of 50% choice between the two rewards. In this model, male and female Wistar rats are trained to press alternate levers to receive either heroin or food reward coupled with a distinct tone or light cue. Rats then undergo a choice phase, wherein reward availability is limited, forcing them to make a mutually exclusive choice between heroin vs. food. Food and water were available ad libitum in the home cage throughout the experiment. Prior to screening candidate therapeutics in this new model, it is critical to establish its predictive validity. Thus, we set out to reverse translate the model using a known therapeutic for opioid use disorder, naltrexone. After three baseline choice sessions, rats underwent seven additional choice sessions following administration of naltrexone (3 mg/kg, 2x/session) or vehicle daily. Naltrexone treatment significantly shifted choice away from heroin in favor of food over time in the overall population. Additional analyses revealed that this effect was carried by the heroin preferring subpopulation only (not food preferers). The day after the last treatment, a relapse test was conducted wherein reward cues/levers were available without rewards. Naltrexone specifically reduced heroin relapse and did not alter response rates for food cues. These results validate and successfully

reverse translate this new preclinical model of heroin choice and relapse. Future studies will employ this model to screen novel therapeutics for opioid use disorder.

TU6. Critical Role for Serotonin in Aversive Effects of Cocaine

*Ying Chao, Jeffrey Parrilla-Carrero, Maya Eid, Peter Vento, Thomas Jhou**

Cocaine produces strong rewarding responses that drive its abuse potential, but also produces aversive effects that modulate this abuse potential, and may underlie individual differences in susceptibility to cocaine addiction. Our lab previously showed that activation of the rostromedial tegmental nucleus (RMTg) by cocaine critically drives cocaine conditioned avoidance. We now show using RNAseq that 80% of RMTg neurons expresses mRNA for the serotonin 2C receptor (protein name 5-HT2CR, gene name htr2c). Because cocaine binds to both serotonin and dopamine uptake transporters, we postulate that these receptors are are a novel mechanism underlying cocaine's aversive effects. Most htr2c positive neurons express markers of RMTg neurons, such as gad1 and foxp1, and a high proportion of them responds with elevated cfos to aversive stimuli. We then found that injection into the RMTg of Ro60-0175, a specific 5-HT2CR agonist, induces conditioned place aversion and enhance anxiety-like behavior, while pharmacological or shRNA blockade of RMTg 5HT2CRs (via the antagonist SB-242084, or shRNA knockdown), reduce cocaine-induced anxiety like behavior, block cocaine conditioned place aversion, and attenuate cocaine conditioned avoidance. Using Sprague Dawley rats that have exhibit either low versus high avoidance responses to cocaine, we find knockdown of htr2c at the RMTg increases cocaine self-administration and reinstatement in "high cocaine-avoider" but not "low cocaine-avoider animals". Further, using slice electrophysiology techniques, we find both cocaine and 5-HT2CR agonist induce depolarization of RMTg neurons that can be blocked by specific antagonist and htr2c specific shRNA. These evidences support an important role of RMTg 5-HT2CR in the aversive effects of cocaine, and the notion that aversive effects of cocaine modulate subsequent relapse to drug seeking. The current studies may identify a valid target for treating cocaine’s aversive effects and relapse drug seeking.

TU7. Neuroinflammation in the Prefrontal Cortex and Striatum Induced by Repeated Binge-Like Intake of the Synthetic Cathinone Methyledioxypyrovalerone (MDPV): Comparison With Methamphetamine

*Erin Nagy, Paula Overby, Lauren Hood, Jonna Leyrer-Jackson, M. Foster Olive**

The neuroinflammatory effects of traditional psychostimulants such as cocaine and methamphetamine (METH) have been examined in detail, but the effects of novel psychostimulants such as the synthetic cathinone methylenedioxypyrovalerone (MDPV) have not been well characterized. In this study, we examined expression profiles of neuroinflammatory markers within the frontal cortex and striatum induced by MDPV, which has long-acting cocaine-like monoamine reuptake inhibiting properties. For comparison purposes, we also examined effects of the monoamine releasing psychostimulant METH. Male and female rats were allowed to intravenously self-administer either MDPV (0.05 mg/kg/infusion), METH (0.05 mg/kg/infusion) or saline in

three binge-like access sessions, each 96-hr in length and separated by 72-hr of forced abstinence in the home cage. Three weeks following the last binge access session, the prefrontal cortex (PFC) and striatum were harvested for multiplex ELISA analyses of various cytokines. In separate groups of animals, brains were obtained for immunohistochemical analyses of microglial and astrocyte density as well as leukocyte infiltration. In both male and female rats self-administering METH, we observed increased levels of MCP-1, CX3CL1, INF-gamma, IL-6, and IL-18 in both the PFC and striatum as compared to animals self-administering saline. In rats self-administering MDPV, we observed an increase in levels of only IL-6 in the PFC and striatum of males, and in the PFC of females, IL-6 levels were decreased. No differences in microglial or astrocyte density in either region were observed as a result of METH or MDPV self-administration, though some evidence of leukocyte infiltration within the PFC was observed. Thus, binge-like intake of METH and MDPV appears to induce neuroinflammatory signaling in the PFC and striatum which is evident 3 weeks into abstinence, and the magnitude and directionality of these effects are dependent on sex and type of psychostimulant.

TU8. Distinct Activity in Reward Neurocircuitry in a Rodent Model of Cocaine-Alcohol Polysubstance Use

Javier Mesa, Yasmin Padovan-Hernandez, Lori Knackstedt*

Despite the prevalence cocaine-alcohol polysubstance use (PSU), there is a lack of preclinical research on this topic. Our previous work developed a rodent model of sequential cocaine-alcohol self-administration which revealed that PSU induces distinct neuroadaptations. We found that while nucleus accumbens core glutamate release accompanies the reinstatement of cocaine-seeking in rats that self-administer cocaine alone, it does not in rats self-administering both cocaine and alcohol. Furthermore, ceftriaxone does not attenuate reinstatement after cocaine-alcohol self-administration and c-Fos analysis reveals distinct neurocircuity involved in such reinstatement. Here, we sought to determine whether such differences arise from pharmacological tolerance or sensitization to a priming dose of cocaine. For 12 days, male Sprague Dawley rats underwent 2 hrs of daily intravenous cocaine self-administration (1mg/kg/infusion) immediately followed by 6 hrs of either two-bottle choice with unsweetened alcohol (20% v/v) and water or water alone. Thereafter, rats underwent daily 2 hr instrumental extinction training without access to alcohol for 2-3 weeks. On the final 5 days of extinction, half of the rats in each condition received ceftriaxone (200 mg/kg IP) while the other half received vehicle. Rats then received a non-contingent cocaine injection (10 mg/kg, IP) and were placed in the operant chamber for 2 hrs without access to cocaine-associated cues and levers, followed immediately by perfusion. Brains were processed for immunohistochemistry to compare cocaine-induced c-fos expression across cocaine+alcohol and cocaine+water groups, as well as differences between ceftriaxone- and vehicle-treated rats. Results suggest that alcohol and ceftriaxone interact to produce divergent changes in c-fos expression across key brain regions implicated in cocaine addiction, specifically increasing BLA c-fos expression. However, no group differences were observed in several brain regions of interest (e.g. nucleus accumbens), indicating that the process of reinstatement, and not the cocaine priming injection, produce different patterns of neural activity in this model.

TU9. Examining Social Behavior in a Mouse Model for Fragile X Syndrome

Corinne Kelly, Abigail Ingram, Laura Smith*

Fragile X Syndrome (FXS), caused by an error in the Fmr1 gene, which prevents its translation, is the leading known single-gene cause of autism spectrum disorder (ASD), with 46% of patients with FXS also diagnosed with ASD. One of the core features of ASD is a deficit in social function, composed of withdrawal, social anxiety, poor eye contact, decreased reinforcement from social engagement, and increased aggression. These symptoms are stressful and impede the ability to participate in everyday activities. Current treatment options are largely behavioral and typically require large amounts of time and effort, and efficacy can be uncertain. Preclinical research on FXS often relies on the use of the Fmr1 knockout mouse model, which has been used widely and successfully. Despite this, social behavior in this mouse model remains relatively understudied, likely due in part to the difficulty of collecting and quantifying such data in an efficient manner. These issues have led to reliance on simplistic testing that may not capture enough detail to make accurate assessments of behavior. Recent advances in machine learning have made detailed scoring more accessible. Using the free, open source software DeepLabCut and SimBA, we are able to examine a large number of discrete behaviors during free interaction between two mice in an open field. These behaviors are categorized into social and nonsocial behaviors, and social behaviors are further categorized into aggressive and nonagressive behaviors. Previous literature has found that changes in frequency and duration of behaviors in each category have specific neural correlates. By comparing this detailed behavioral data to traditional measures of social behavior such as the social preference test and tube dominance test, we predict that we will be able to determine which behaviors contribute to the overall phenotype found in FMR1 KO mice, and identify neural targets for future research.

TU10. CCR2 Monocytes Repair Cerebrovascular Damage Caused by Chronic Social Defeat Stress in Mice

Miles Herkenham, Joshua Samuels, Stacey Kigar, Chelsie Poffenberger, Michael Lehmann*

Mental disorders such as major depressive disorder (MDD) have a complex etiology. Genetic, biological, and environmental factors contribute to their manifestation. A contributing environmental factor is psychosocial stress. In animals, psychosocial stress can be studied using a paradigm called chronic social defeat (CSD). CSD in mice elicits depressive-like behaviors, elevated activity of microglia, and scattered cerebral microbleeds with associated local blood-brain barrier (BBB) breakdown. The peripheral immune system plays an important role in response to and resolution of the injury. We investigated the participation of innate immune cells—monocytes—during CSD and after cessation of CSD. We measured activated CCR2hi monocyte trafficking to the vascular injury sites in Ccr2 reporter mice both during two weeks of CSD

and one week following CSD cessation (CSD recovery). We found that CSD induced stochastically scattered rare microhemorrhages. The microbleeds were microscopically identified by leaked i.v.-injected tracers and by plasma immunoglobulin and fibrinogen and erythrocytes located in perivascular spaces. Nevertheless, CSD did not recruit additional monocyte infiltration to these sites. However, after recovery from CSD, many newly adhered CCR2+ cells were detected in perivascular spaces. Flow cytometry showed that adhered CCR2+ cells were mostly the anti-inflammatory Ly6C-lo type, and confocal microscopy showed they phagocytosed fibrinogen. Depletion of monocytes with i.p.-injected clodronate liposomes during CSD recovery prevented fibrinogen clearance and blocked behavioral recovery in the urine scent marking task. We hypothesize that peripheral CCR2+ monocytes play no role during chronic psychosocial stress. However, during the stress recovery period, chemokine signaling permits anti-inflammatory monocytes to lodge in perivascular spaces, phagocytose blood products, and support vascular repair, promoting normalization of behavior post stress.

TU11. A Comprehensive Ethogram of Rat Behavior Across Pavlovian Fear Discrimination

Amanda Chu, Christa Michel, Nicholas Gordon, Katherine Hanrahan, Aleah DuBois, David Williams, Michael McDannald*

In Pavlovian fear conditioning, a neutral cue is paired with an aversive stimulus, such as foot shock delivery. One result of this predictive relationship is that cue presentation will elicit a suite of defensive behaviors. The most commonly studied defensive behavior is freezing, a 'passive' behavior defined by the absence of movement. Recent studies have revealed that danger cues can elicit 'active' defensive behaviors, characterized by increased movement. The goal of the current study was to construct a complete ethogram of rat behavior across Pavlovian fear discrimination. We tested 24 rats (12 females) in a conditioned suppression procedure. Rats were trained to nose poke for food rewards, then received 16 discrimination sessions in which three auditory cues predicted unique foot shock probabilities: danger (p=1.00), uncertainty (p=0.25), and safety (p=0.00). Poke-reward and cue-shock contingencies were independent. We captured images at a rate of 5 frames/s before and during cue presentation (5 s pre-cue, 10 s during cue). Initial analyses reveal a mixture of passive (e.g. freezing and stretching) and active behaviors (e.g. rearing, locomotion, jumping, and scaling). Across all sessions, active defensive behaviors accounted for 35% of all behaviors, passive defensive behaviors for 16%, food cup for 23%, and nose poke for 26%. We will present a complete ethogram over cue presentation and across the 16 fear discrimination sessions. Additionally, we will scrutinize our findings for sex differences and for quantitative and qualitative differences in behavior elicited by danger and uncertainty cues. Our hand-scoring efforts will reveal fine organization of behavioral responding and form the basis of a data set to train neural networks for behavior classification. Successful application of neural networks to behavior classification will permit highly-detailed, large-scale analysis of behavior to reveal neural circuits supporting diverse threat behavior.

TU12. Effects of 3 Months Reduction in Myostatin Levels: Age and Sex Differences

Sonsoles de Lacalle, Dallin Tavoian, Nick Lozier*

Given the expected increase in number and relative proportion of adults aged 65+ in the US and throughout the world, there has been renewed interest in identifying healthspan modifiers. The similar aging patterns of mice and humans and the relatively short lifespans of mice make them a useful option to test novel interventions to slow or reverse the aging process. Reducing myostatin (MSTN) levels has therapeutic potential to target age-related declines in muscle size and strength. Since its discovery in 1995, several studies have confirmed the hypertrophic and hyperplasic effects of MSTN reduction. Post-developmental reduction in MSTN, a more applicable model for translation to an aging human population, produces similar but muted hypertrophic effects, and no hyperplasia has been reported; furthermore, it remains unclear at what age treatment should be initiated to obtain maximal benefit. To address this question in the present work we reduced MSTN levels for three months in young (4 months) and middle-aged (12 months) mice and tested for changes in strength and balance.
There was a significant three-way interaction ($p = 0.034$) on percent change in absolute rear grip strength but not in front limb strength. We also found maximal forelimb grip strength at four months of age, but maximal hind limb grip strength at 15 months of age. There was also an effect of sex, with young female mice overall stronger than their male counterparts ($p = 0.001$). The female experimental group of mice had reduced rear grip strength in young ($p = 0.004$) compared to aged-matched controls. This sex-dependent difference was not present in the middle-aged group ($p = 0.45$). Measures of balance (Rotorod) remained stable throughout the experiment.

Humans tend to lose muscle mass and strength at a greater rate in the lower extremities, and lower extremity strength is a better predictor of functional performance than upper extremity strength. Based on our results, mice appear to lose strength in a similar pattern. Reduced hind limb strength with age in mice may be associated with the reduced rearing activity that has previously been reported and could result in greater dependence on the forelimbs to support body weight.

TU13. An Instability Mechanism for Frequency Coupling of Mesoscopic Activity in the Hippocampus

*Yu Qin, Alex Sheremet**

Oscillatory patterns observed in LFP traces exhibit cross-frequency coupling (CFC, e.g., theta/gamma coupling, and sharp-wave/ripples). Because these oscillations represent mesoscopic patterns of brain-activity supported by recurrently neuron connections (Muller et al., 2018; Edelman, 1987), it is natural to ask whether mesoscopic field models such as the Wilson-Cowan equations (Cowan et al., 2016) that ignore the details of the dynamics of cell individuals, support the CFC process. Here, we investigate the CFC problem using a generalization of the Wilson-Cowan equations proposed by (Qin et al., 2020), restricted to excitatory neurons. The basic CFC mechanism may be described as a destabilization of high-frequency oscillations forced by the low frequency component. We examine the properties of linear approximations of the solutions and investigate the full nonlinear

system through numerical simulations. The cross-frequency coupling process supported by the mesoscopic model is consistent with observations: bispectra of the solutions of the governing equations exhibit bands of theta-gamma coupling similar to bispectra of LFP traces recorded in running rats Sheremet et al. 2019. The mechanism responsible for the CFC process is the intrinsic nonlinearity of the system of governing equations. Remarkably, the cross-frequency coupling emerges without the participation of a second type of neural field (e.g., inhibitory). However, we demonstrate that inhibition, in this case in the form of refractoriness, is fundamental to this process. While the consensus is that the dominant mechanism of theta-gamma coupling is either driven by pyramidal interneuronal network or an interneuronal network architecture (e.g., Segneri et al., 2020), the instability mechanism identified here might play a role in the initiation of this interaction.

TU14. Endocannabinoids Control the Neural Substrates of Interval Timing in the Nucleus Accumbens

Natalie Zlebnik, Joseph Cheer*

Background: Cannabinoids disrupt timing by interfering with dedicated brain timing circuits. The ability to perceive and respond to temporally relevant information in the environment is critical for adaptive survival, and corticostriatal circuits play a central role in timing behavior. Our previous work demonstrated that phasic dopamine release in the nucleus accumbens (NAc) encodes interval timing and that CB1 receptor activation accelerates the perception of time and shifts temporally-engendered patterns of phasic dopamine release. Methods: Using in vivo optogenetics and neuronal ensemble recordings, we examined how endocannabinoid signaling orchestrates timing-mediated NAc network dynamics in male mice. Results: We found that interval timing was encoded by bidirectional ramping activity of NAc ensembles and progressive increases in gamma frequency power of the local field potential. Increasing levels of the endocannabinoid 2-AG via the MAGL inhibitor JZL184 (18 mg/kg, ip) resulted in an acceleration of time estimation and attenuation of interval encoding in a CB1 receptor-dependent manner. Additionally, endocannabinoid-mediated disruptions in interval timing were occluded by optically-driven NAc network oscillations at gamma frequencies. Conclusions: These results reveal a significant role for endocannabinoids in the accumbal network dynamics that guide timing behavior and may have important implications for the use of pharmacotherapies targeting the endocannabinoid system and for the recreational use of plant-based and synthetic cannabinoids.

TU15. Disruption of the Proinflammatory Environmental Milieu by Adolescent Ethanol Exposure Adversely Impacts Adult Hippocampal Neurogenesis and Spatial Navigation in Male and Female Rats

Victoria Macht, Natalie Elchert, Rachael Fisher, Ryan Vetreno, Fulton Crews*

Binge ethanol exposure during adolescence period produces persistent decreases in adult hippocampal neurogenesis and deficits in cognitive flexibility related behavioral tasks. Specifically, our rat studies find that adolescent intermittent ethanol (AIE; 5 g/kg/day

ethanol or water, i.g., 2-day on/2-day off cycle from postnatal day PND25-55) exposure induces persistent increases in the chemokine C-C motif ligand 2 (CCL2), high mobility group box protein 1 (HMGB1), phosphorylation of nuclear factor kappa B p65 (pNfκB), and cyclooxygenase-2 (COX-2) in the adult dorsal hippocampus in males. We have recently expanded upon these findings by testing the hypothesis that inhibition of AIE-induced proinflammatory signals in adult male and female rats by the non-steroidal anti-inflammatory compound indomethacin [4.0 mg/kg/day indomethacin or vehicle (0.5% carboxymethylcellulose)] can both prevent and reverse loss of neurogenesis in adulthood. Results indicate that AIE decreased adult (P71) hippocampal DCX+IR by 35% in males and 28% in females relative to water-treated controls. AIE also increased adult hippocampal HMGB1+IR by 150% in males and 199% in females and COX-2+IR by 180% in males and 173% in females relative to water-treated controls. Following indomethacin treatment, HMGB1+IR and COX-2+IR were attenuated to levels not significantly different from water-treated controls, and similarly levels of DCX+IR were restored to levels comparable to water-treated controls. These molecular changes in the hippocampus were accompanied by AIE-induced deficits in acquisition (females) and reversal learning (males and females) in a Morris water maze task. Indomethacin treatment attenuated acquisition deficits in spatial navigation evidenced in AIE females and restored reversal learning in both sexes. These data suggest that AIE's persistent disruption of the hippocampal neurogenic niche is a critical mediator of long-term deficits in cognitive flexibility in both sexes. Supported by the Neurobiology of Adolescent Binge Drinking in Adulthood (NADIA) consortium of the NIAAA (U24 AA020024, U01 AA020023) and the Bowles Center for Alcohol Studies (P60 AA011605). Also Funded by T32 AA007573, and K01 AA025713 (RPV).

TU16. Funcitonal Connectivity in Children and Young Adults With Mild TBI

*Ben Rasmussen, Berlinda Ofori, Axel Lichtenberg, Cooper Hodges, Rebecca Lundwall**

Background: Mild traumatic brain injury (mTBI) is classified as a loss of consciousness, confusion, or disorientation for less than 30 minutes after a blow to the head or body Understanding consequences of mTBI in children and young adults is critical because brains are developing until about 30 years old, depending on the metric. Cognitive impairment, including problems with memory and attention are common sequelae. Reduced cognitive performance has been shown to lead to academic difficulties, behavioral problems, and stress in the child and family.
Methods: Our goal is to understand differences in brain connectivity in attention networks between individuals with a mTBI and healthy controls. To meet this goal, we invited 50 children and young adults to be scanned. Two individuals were excluded for poor quality scans.

The participants in this study (n=48) consisted of those with a history of mild TBI (n=23; aged 7-24 years old, M = 18 years; 44% male) and who were 3- 18 months post-injury and age- and sex-matched controls with no history of head injury (n=25; aged 8-24 years old, M = 18 years; 44% male). We obtained structural scans (T1, T2), diffusion-weighted scans

(DTI), and a resting state functional scan to test resting state functional connectivity (rsFC). All MR imaging data was acquired at the Brigham Young University MRI Research Facility in Provo, Utah on a Siemens Tim Trio 3 Tesla whole-body MRI scanner, for which a body coil was used for transmission and a 32–element head coil for reception. Each participant also completed health history questionnaires and the NIH Toolbox Cognition battery, as well as a task measuring reflexive (orienting) attention. Tasks were used to assess neurocognitive functioning as well as personal and family stress.

Results: We compare functional connectivity in two brain networks using two regions located in dorsal attention network (the intraparietal sulcus and the frontal eye fields) and two regions in the ventral attention network (the temporoparietal junction and the orbital frontal cortex). We find similar connectivity in control participants within each network than in case participants. Neither cases nor controls demonstrated altered connectivity between networks. We also explore differences between groups in terms of neurocognitive functioning and personal and family stress.

TU17. Step-Wise Disassembly of GABAergic Synapses During Pathogenic Excitotoxicity

Joshua Garcia, Sara Gookin, Kevin Crosby, Samantha Schwartz, Katharine Smith*

GABAergic synaptic inhibition controls neuronal firing, excitability and synaptic plasticity to control neuronal circuits. Following an acute excitotoxic insult, inhibitory synapses are eliminated, reducing synaptic inhibition, elevating circuit excitability, and contributing to the pathophysiology of brain injuries. However, mechanisms that drive inhibitory synapse disassembly and elimination are undefined. We find that inhibitory synapses are disassembled in a sequential manner following excitotoxicity: GABAARs undergo rapid nanoscale rearrangement and are dispersed from the synapse along with presynaptic active zone components, followed by the gradual removal of the gephyrin scaffold, prior to complete elimination of the presynaptic terminal. GABAAR nanoscale reorganization and synaptic declustering depends on calcineurin signaling, whereas disassembly of gephyrin relies on calpain activation, and blockade of both enzymes preserves inhibitory synapses after excitotoxic insult. Thus, inhibitory synapse disassembly occurs rapidly, with nanoscale precision, in a step-wise manner, and likely represents a critical step in the progression of hyperexcitability following excitotoxicity.

TU18. β-Amyloid Deposits in a Young Covid Patients

C. Harker Rhodes, David Priemer, James Goldman, Daniel Perl*

A 58-year-old woman who died of COVID infection was included as a control subject in an ongoing autopsy study of the neuropathology of military traumatic brain injury. An immunohistochemical stain for β-amyloid done only because that stain is done on all the cases in the TBI study resulted in the serendipitous observation of numerous β-amyloid deposits in the neocortex of this relatively young woman with no significant neurologic history. The immunohistochemical study was replicated in a second laboratory using a different anti-amyloid monoclonal antibody with the same result. We intentionally describe the β-amyloid accumulations as "deposits", rather than "plaques" because although in both immunohistochemical studies the deposits were histologically similar to diffuse β-amyloid

plaques, they were thioflavin negative. We speculate without proof that these "deposits" may be the pathophysiologic precursors of "plaques" and that at this early stage in their evolution, before they have substantial beta pleated sheet structure, they may be reversible. This histologic finding appears to be common in young patients with fatal COVID infections – we subsequently found it in several autopsies of COVID patients younger than 60 y/o – and we speculate that it may be related to COVID encephalopathy and/or the increased incidence of cognitive impairment in COVID survivors. This histologic finding is not, however, COVID-specific – we have made similar observations in autopsy material from young patients who died hypoxic deaths due to respiratory infections in the pre-COVID era and in occasional autopsies of young patients with traumatic or other brain injuries.

TU19. Nrf2 in the RGCS Modulates Glaucoma Pathogenesis Onset and Severity

Sarah Naguib, Jon Backstrom, Elisabeth Artis, Purnima Ghose, John Ang, Tonia Rex*

NRF2, a transcription factor that modulates a cell's response to reactive oxygen species (ROS), has been implicated as a therapeutic target in models of neurodegeneration including glaucoma. We previously demonstrated that an NRF2 mediated endogenous antioxidant response occurs at 2-weeks post-IOP elevation, which is one week after ROS elevation and weeks prior to detectable pathology in the microbead occlusion model of glaucoma (MOM). The goal of this study was to determine if NRF2 was activated within the retinal ganglion cells (RGCs) or astrocytes. We intravitreally injected Nrf2fl/fl mice with AAV2/2.mSncg.Cre to knock-down Nrf2 specifically within the RGCs, and then elevated the IOP using the MOM and assessed the endogenous antioxidant response at 2-weeks and pathology at 5-weeks. The RGC-specific Nrf2 KO mice had a greater increase in nitrotyrosine labeling in the RGC layer, a marker for ROS, compared to mice injected with the control AAV, AAV2/2.CMV.eGFP. There was also a 33% decrease in levels of PRDX6 and a 35% decrease in levels of SOD3 in RGC-specific Nrf2 KO mice in comparison with AAV2/2.CMV.eGFP injected controls, which are two prominent antioxidants mediated by NRF2-dependent and independent mechanisms. At 5 weeks post-IOP elevation, the RGC-specific Nrf2 KO mice had a 37% decrease in their photopic negative response (PhNR) amplitude and a 26% decrease in the VEP amplitude in comparison to AAV2/2.CMV.eGFP injected controls. Further, overexpression of Nrf2 in ganglion cell layer neurons by intravitreal injection of AAV2/2.CMV.Nrf2 resulted in lower superoxide levels, preserved amplitude of the PhNR, and decreased axon degeneration. Together, these data suggest that the endogenous Nrf2/ARE mediated protective response is driven, at least in part, by the RGC localized NRF2. Further, RGC-directed Nrf2 over-expression is a viable therapeutic approach that should be explored further.

TU20. Inverse Neurovascular Coupling Contributes to Positive Feedback Excitation of Vasopressin Neurons in Response to a Systemic Homeostatic Challenge

Javier Stern, Ranjan Roy, Ferdinand Althammer, Jordan Hamm, Vinicia Biancardi, Jessica Filosa, Colin Brown*

Neurovascular coupling (NVC), the process that links neuronal activity to cerebral blood flow changes, has been mainly studied in superficial brain areas, namely the neocortex. Whether the conventional, rapid and spatially restricted NVC response can be generalized to deeper, and functionally diverse brain regions remains unknown. Implementing an approach for in vivo two-photon imaging from the ventral surface of the brain, we show that a systemic homeostatic challenge, acute salt loading, progressively increases hypothalamic vasopressin (VP) neuronal firing and evokes a vasoconstriction that reduces local blood flow. Vasoconstrictions are blocked by topical application of a VP receptor antagonist or tetrodotoxin, supporting mediation by activity-dependent, dendritically-released VP. Salt-induced inverse NVC results in a local hypoxic microenvironment, which evokes positive feedback excitation of VP neurons. Our results reveal a novel physiological mechanism by which inverse NVC responses regulate systemic homeostasis, further supporting the notion of brain heterogeneity in NVC responses

TU21. Investigating a Potential Role of Cspgs in Neuronal Differentiation of Cultured Adult Stem Cell Populations

Jeffery Plunkett, Karina Medina, Sandy Benito, Kenel Joseph Jean Pierre, Andrew Pardo, Martin Oudega*

In the mammalian central nervous system (CNS), neurons fail to regenerate their axon after injury due at least in part to the presence of growth-inhibitory molecules such as chondroitin sulfate proteoglycans (CSPGs). However, adult zebrafish (Danio rerio), contain certain CNS neuronal populations that regenerate their axon after an injury in the presence of CSPGs. Furthermore, it is well documented that adult zebrafish retain multiple proliferative neurogenic and stem cell niches to enable growth and repair of CNS tissues. Based upon these findings, one can hypothesize about the possible roles of CSPGs and stem cells in the observed CNS regenerative abilities seen in teleost fish. Our results demonstrate a potential role for CSPGs in the differentiation of stem progenitor cells into neurons. To investigate the role that CSPGs may play in the differentiation of stem cell populations, we developed and characterized a primary culture system from adult zebrafish brain. This heterotypic culture contains neurons, glia, and a large population of stem/progenitor cells. Substrate adhesion and free-floating, rotating aggregate, CNS cellular cultures were used to examine the role CSPGs play in axonal outgrowth of maturing neurons and the differentiation of stem/progenitor cells. In analyzing various markers for axonal outgrowth and differentiation in both culture systems, our data indicate that CSPGs do play a role in both processes. We are currently using a combination of immunocytochemical and statistical analyses to gain a better understanding of the roles that CSPGs play in guiding stem cell fate and neuron axonal regeneration.

TU22. Prior Experience With Behavioral Control Over Stress Facilitates Social Dominance

Gabriel Costanza-Chavez, Phillip Coleman, Garrett Potter, Connor McNulty, Rory Sanchez, Simone Mellert, Steve Maier, Michael Baratta*

The degree of control an organism has over an adverse event potently modulates its outcome. Instrumental control over some aspect of a stressor (e.g. its termination) prevents the numerous neurochemical and behavioral changes that occur following a physically identical uncontrollable stressors. Instrumental learning can occur through one of two circuits: the medial prefrontal cortex-dependent act/outcome (A/O) system or the dorsolateral striatum (DLS)-mediated habit system. Research indicates that both the prelimbic (PL) region of the medial prefrontal cortex and the dorsal medial striatum (DMS) are necessary for the protective effects of control, supporting the idea that behavioral control is learned through the A/O system. We have recently found controllable stress (Escapable Shock; ES) facilitates later dominance during a warm spot competition task (solely occupy a single warm spot on a cold cage floor more often, i.e. the Warm Spot Test) compared to subjects that received physically identical uncontrollable stress (inescapable shock; IS) or no-stress (home cage; HC). This dominance-inducing effect of ES was present in males but not females. Intra-PL pharmacological inhibition at the time of ES (GABA agonist muscimol 50ng/hemisphere) led to later reduced dominance in male ES subjects. Others have shown the necessity of PL activation for repeated winning in a motivated competition, so we next decided to investigate the necessity of the PL for repeated winning in the warm spot test in stress naïve animals. We found that inhibition of the PL with the GABA agonist muscimol (50ng/hemisphere) resulted in an immediate loss of dominance. Similarly, inhibition of the DMS with the NMDA antagonist AP5 (0.5µL of 30 mM solution/hemisphere) also resulted in an immediate and lasting loss in dominance. This data suggests that the PL is critical for winning because it participates in a corticostriatal system that allows action-outcome knowledge to guide future effortful behavior.

TU23. Leveraging Transfer Learning for Identification and Quantification of Neuronal Biomarkers in Microscopy Images.

*Jacob Theis, Grant Wade, Will O'Keeffe, Kristy Lawton, John Harkness**

Many fields of neuroscience utilize microscopy imaging to evaluate experimental outcomes and infer relationships between relevant biomarkers. Unfortunately, the ability to identify and quantify these biomarkers remains a bottleneck, often requiring significant hand annotation that is both time consuming and potentially introduces intra and inter-rater error. While computer vision has emerged as an excellent solution to accurately detect regions of interest in microscopy images, the training of deep machine learning models generally requires 100,000s of user annotations. Although hand-annotation is a large upfront time investment, it produces a highly accurate model that is useful long-term for much faster and more consistent analysis of frequently studied biomarkers. Regrettably, this method is less useful for researchers studying a novel cell type or biomarker with few training images available. To combat these limitations, we used a machine learning technique known as transfer learning, to develop object detection capabilities for novel biomarkers using previously trained models and only 10s of newly annotated images. We

tested several different transfer learning methods with two of our existing neural biomarker models, including wisteria floribunda agglutinin (WFA) and Parvalbumin (PV), to create new customized versions for different research labs. Our results indicated that several transfer learning methods worked well, with one performing consistently better than the others. We then tested this best method on a small number of androgen receptor (AR) images, a biomarker for which we did not have an existing base model, and reached accuracy scores comparable to our original models for other biomarkers. Overall, by utilizing transfer learning we were able to reduce the number of required annotated images from several 1000s to dozens or less, with comparable or improved detection accuracy. Our results indicate that this computational method will greatly reduce time and resources needed to train accurate object detection models, thus broadening the reach of smart automated analysis to novel biomarkers and smaller research labs. Overall, this technology will allow the analysis bottleneck to catch up to the current hardware advances in the field, and rapidly advance neuroscience research progress.

TU24. Positive and Negative Modulators of Nmda Receptor Function Act via Linker Regions Connecting Agonist Binding to the Channel Gate

Elijah Ullman, Russell Fritzemeier, Dennis Liotta, Srinu Paladugu, Stephen Traynelis*

Our lab has previously reported on a series of first-in-class (EU-1622 and 1794 series), conductance-modifying NMDA receptor specific positive and negative allosteric modulators (PAM and NAM). EU-1622 PAMs as well as -1794 series PAMs and NAMs reduce calcium permeability in addition to unitary conductance and enhance glutamate and glycine potency. We have recently identified NAMs within the EU-1622 series that decrease single channel conductance, open probability, mean open time, and enhance glutamate and glycine potency. The mechanism of action and structural determinants underlying the conductance-modifying effects of either EU-1622 or -1794 series are incompletely understood and we are actively identifying these mechanisms. Due to the reduction in calcium permeability in the series of positive allosteric modulators, the negative allosteric modulators may prove beneficial in the treatment of disease states where calcium influx exacerbates neurological deficits, such as in stroke or traumatic brain injury.

TU25. Responding to Predicted and Surprising Foot Shock Outcome in Ventral Pallidum and Nucleus Accumbens Core

Mahsa Moaddab, Madelyn Ray, Michael McDannald*

The ventral striatopallidal system, a basal ganglia network, includes the ventral pallidum (VP) and the nucleus accumbens. The involvement of different nodes within the ventral striatopallidal system in mediating reward has been well-studied, yet little is known about the contribution of such circuitry to threat processing. Recently, we reported the VP and nucleus accumbens core (NAcc) as neural sources of threat signals. We did this using a discrimination procedure consisting of cues predicting unique foot shock probabilities: danger (p = 1.00), uncertainty (p = 0.25), and safety (p = 0.00). We showed dynamic relative threat signaling during cue presentation within the VP, and specific threat signaling within the NAcc. Here, our aim was to examine firing patterns following the delivery and omission of foot shock outcomes in each region. We observed diverse neural signals for aversive outcome in each region. Further, we found the VP and NAcc to be composed of very similar functional neuron types. Many VP and NAcc neurons are shock responsive, showing equivalent responding following danger and uncertainty shock. However, many other VP and NAcc show differential firing to surprising and predicted foot shock on uncertainty shock and danger trials. This firing pattern is indicative of positive prediction error – a signal to strengthen cue-shock associations. Additionally, both the VP and NAcc contain neurons showing differential firing to surprising and predicted foot shock omission on uncertainty omission and safety trials. This firing pattern is indicative of negative prediction error – signal to weaken cue-shock associations. Neither regions contain a substantial number of neurons showing a fully signed prediction error. Our observation of similar aversive outcome responding raises the possibility that both the VP and NAcc receive inputs from the same areas involved in foot shock-related processing. A complete analysis of VP and NAcc outcome firing will be presented.

TU26. ClearScope: Image Large and Small Intact Brains Using Light Sheet Theta Microscopy

Aidan E. Sullivan, Peter J. Lang, David S. Denu, Benjamin W. Haydock, George C. Thomas, Nathan J. O'Connor, Brian S. Eastwood, Ithiel M. Macfarlane, Raju Tomer, Paul J. Angstman, Jacob R. Glaser*

Through recent advancements in tissue clearing techniques and Light Sheet Microscopy (LSM), brain-wide exploration of connectivity and phenotypic profiles of behavior and pathological states is now attainable. To improve on existing LSM technologies, we collaborated with the Tomer laboratory at Columbia University to develop ClearScope – an angled, dual light-sheet microscope that produces high-resolution images of large, intact specimens while minimizing photo-damage and out of focus features. Utilizing revolutionary Light Sheet Theta Microscopy (LSTM), ClearScope applies two light sheets, oblique to the specimen and detector axes, to image tissue specimens of extraordinary sizes, such as slabs from human and other primate brains as well as whole rat and mouse brains, at high resolution with no lateral limitations. ClearScope is commercially available for research laboratories using tissue clearing techniques that need a robust multi-channel imaging solution. Its modular hardware design enables configuration of a variety of magnifications (4x-25x) and up to seven laser excitation wavelengths. The intelligent

refractive index compensation makes this microscope compatible with nearly all clearing techniques. Additionally, ClearScope is equipped with a wide-field fluorescence imaging mode for high-speed evaluation of the specimen, providing a contextual preview prior to high-resolution light-sheet acquires of subregions. Recent software and hardware enhancements have resulted in unprecedented axial resolution and uniform illumination throughout the specimen. Automated algorithms have been implemented to stitch volumes in real-time, streamlining the image acquisition/compilation process. These optimizations contribute to a simple and comprehensive user experience, minimal required training time, and generation of diverse file format outputs for downstream analysis. ClearScope's unique hardware configuration and intuitive software make it an industry-leading solution for cleared tissue imaging.

TU27. Chronic Morphine Has Opposing Effects on Opioid Sensitivity of Glutamatergic Thalamo-Striatal and Thalamo-Cortical Terminals

Elizabeth Jaeckel, Alberto Perez-Medina, Erwin Arias-Hervert, Yoani Herrera, Stefan Schulz, William Birdsong*

Opioids mediate pain relief and reward primarily through activation of the μ-opioid receptor (MOR). Prolonged opioid use results in tolerance to pain relief, but the cellular adaptations that drive tolerance are not well understood. Glutamatergic projections from the mediodorsal thalamus (MD) to the striatum and anterior cingulate cortex (ACC) are involved in transmission of affective pain, or the aversive component of pain. MORs are present on presynaptic MD terminals in the striatum and ACC, but regulation of presynaptic MORs has not been well studied. Phosphorylation is thought to regulate MOR signaling. Upon activation, MORs are phosphorylated at the carboxyl (C)-terminal tail, terminating signaling via associated G-proteins. Phosphorylation has been heavily implicated in tolerance, but it is not clear whether and how it may affect MOR function in presynaptic terminals. This work aimed to determine how chronic opioid exposure alters sensitivity of presynaptic MORs to an opioid challenge at thalamo-cortical and thalamo-striatal terminals, and whether opioid sensitivity is enhanced at these synapses in MOR phosphorylation-deficient mice (10 S/T-A). Postsynaptic currents were recorded in striatal medium spiny neurons and ACC layer V pyramidal neurons in mouse brain slices following optical excitation of MD terminals before and after application of the MOR agonist morphine. In WT mice, chronic morphine resulted in sensitization at thalamo-striatal terminals, where inhibition of neurotransmitter release by morphine challenge was enhanced. In contrast, chronic morphine resulted in tolerance at thalamo-cortical terminals, where inhibition was attenuated. Both sensitization and tolerance were diminished in 10 S/T-A mice, indicating MOR phosphorylation may be involved in driving these effects. The findings of this study may indicate that chronic opioid exposure alters the relative strength of thalamic innervation of ACC and striatum in the continued presence of opioids.

TU28. Euphorbia Bicolor Latex Extract Reduces Mechanical Allodynia in a Rat Model of Thermal Injury

Temiloluwa Olaoluwa, Micheal Paul Hunter, DiAnna Hynds, Camelia Maier, Dayna Averitt*

Burn injury is associated with oxidative stress and prolonged inflammation which can lead to chronic pain. Current treatment for pain associated with burns include oral and intravenous analgesics such as NSAIDs, opioids, and gabapentinoids which have all been linked to undesired side effects. As burns represent a particularly challenging type of injury to treat, novel strategies that mitigate pain related to burns are needed. Our previous studies indicate that the extract of Euphorbia bicolor, a plant native to the southern United States, may provide a novel analgesic as it demonstrates anti-inflammatory, antinociceptive, and antioxidant properties. Phytochemicals in the E. bicolor extract can directly reduce nociceptor activity, reduce proinflammatory cytokines/chemokines, and reduce reactive oxygen species (ROS). Further, E. bicolor latex extract induces long-lasting, non-opioid peripheral analgesia in two rat models of inflammatory pain. As burn pain involves sensory neuron damage, oxidative stress, and inflammation, E. bicolor extract may effectively target each of these mechanisms providing a multimodal therapeutic for treating burn pain. We hypothesized that E. bicolor latex extract will reduce mechanical allodynia in a rat model of pain associated with full thickness thermal injury. Two concentrations of E. bicolor ethanol latex extract, 100 µg/mL and 500 µg/mL, in 0.9% sterile saline, were used. Adult male Sprague-Dawley rats (200-300 g) received a full thickness thermal injury to the plantar surface of the right hind paw by applying a soldering iron tip at 100□C for 30 seconds. Mechanical allodynia was then recorded 24, 48, and 72 hrs post-injury to confirm development of pain behaviors. Rats then received one intraplantar injection of either vehicle or E. bicolor latex extract immediately adjacent to the thermal injury and mechanical allodynia was re-examined at 1, 6, 24, 48, and 72 hrs post-injection then once weekly until the thermal injury resolved. Here we report that mechanical allodynia fully develops at 72 hrs following thermal injury. Peripheral analgesia was then detected within 24 hrs of injection of the 500 µg/mL dose of E. bicolor extract. These data confirm that E. bicolor latex extract contains phytochemicals that evoke potent analgesia in a rat model of burn pain.

TU29. Sex Differences in Stress-Exacerbated Orofacial Pain and Glial Density in Ascending Trigeminal Pain Pathways

Daisy Cantu, Natalia Santos, Erica Rodriguez, Angela Lopez-Ramirez*

Psychological stress exacerbates orofacial pain to a greater degree in women when compared to men. Unfortunately, most preclinical studies investigating stress and orofacial pain are reported in male rodents. It is unclear whether stress exacerbated orofacial pain occurs in females. Probable mechanisms involved in stress exacerbated orofacial pain may implicate astrocytes. Studies indicate that orofacial inflammatory pain and stress influence Glial Fibrillary Acid Protein (GFAP) expression in the brain. We aim to determine whether exposure to sub-chronic stress (the forced swim test; FST) alters sensitivity at the inflamed right vibrissal pad (RVP) and visualize astrocytes in the brainstem of male and female rats. We hypothesized that FST increases orofacial pain behaviors and astrocyte density in

ascending trigeminal circuitry of females. Mechanical sensitivity was recorded in adult Sprague-Dawley male and female rats using the von-Frey method. Rats received one injection of Complete Freund's Adjuvant (CFA) into the RVP. Twenty-four hours later, orofacial allodynia was confirmed. All rats were subjected to either three consecutive days of the FST or sham test. Mechanical allodynia was re-assessed on 1, 4, and 8, and 11 days following the FST or sham paradigms. On day 8, all rats received the trans-synaptic tracer wheat-germ-agglutinin into the RVP. On day 11, mechanical allodynia was re-assessed immediately, followed by perfusion fixation. The trigeminal ganglia and brainstem were extracted and processed for immunohistochemistry. We report that CFA evoked significant mechanical allodynia in the RVP of males and females. Females display greater allodynia one, four, and eight days after FST when compared to males. Inflamed males exposed to the FST expressed more GFAP in the brainstem when compared to sham. Conversely, female brainstem expressed comparable GFAP. Our data indicate sex differences in the effects of stress on mechanical allodynia in the orofacial region.

TU30. Studying Perinatal Risk Factors for Schizophrenia Using a Sibling Birth Cohort

*Nursel Selcukler, Christine Hughes, Brandon Coombes, Matej Markota**

Introduction: Previous studies demonstrated a link between forceps delivery and higher risk of schizophrenia in adult offspring, however, it is unclear if a causal link exists. The goal of the present study is to provide further clarity on this link by using a birth cohort of maternal siblings.

Methods: This will be a case-control study using the Rochester Epidemiology Project records linkage system. The original cohort contained all mother-offspring pairs born in Olmsted County (MN) between 1980-92. Case was defined as any offspring with lifetime diagnosis of schizophrenia/schizoaffective disorder (SZ). Control was defined as a maternal sibling of the case who was never diagnosed with SZ. Data on type of delivery, sex, gestational infections, weeks of gestation, APGAR scores, maternal and paternal age at birth, birth order, and maternal substance use during pregnancy were abstracted from records.

Results: 143 of 15,721 infants in the original cohort were diagnosed with SZ (0.9%). 85/143 SZ cohort members also had a maternal sibling in this cohort, these 85 pairs represent the final cohort here. For preliminary results, data on 16 case-control pairs have been abstracted (19% of the final cohort). 5 of 32 cohort members were delivered via forceps (15.6%), all 5 developed SZ, there were no forceps deliveries in control subjects. Using permutations, we found that the chance of all 5 offspring delivered with forceps in affected-unaffected sibling pairs having SZ was 2.3%.

Discussion: Our preliminary results confirm the forceps-SZ association. While this study will not provide definitive answers, it may narrow down the spectrum of likely explanations. Our preliminary results support either forceps delivery itself and/or a clinical complication necessitating forceps use as a possible driver for this association; our findings do not support previously postulated explanation that mothers with genetic burden for SZ are simply more likely to have forceps deliveries.

W1. Dopaminergic Systems of the Ventral Striatum's Tubular Striatum and Appetitive Responses to Electronic Cigarette Vapor

Natalie Johnson, Theresa Patten, Amanda Dossat, Mariella De Biasi, Minghong Ma, Daniel Wesson*

Adolescent use of nicotine-containing electronic cigarettes (e-cigs) has dramatically increased in recent years. Along with nicotine, e-cigs often possess additional additives, with fruit additives being the most popular among adolescents. These additives are a primary reason for e-cig experimentation (i.e., vaping) in young people, and have been shown to potentiate nicotine reward and reinforcement in both humans and rodents. The volatile odors of e-cigs are of particular importance to the sensory perception of vaping and subsequent adolescent enjoyment. However, the mechanisms by which e-cig odors influence nicotine intake are unknown. The brain's tubular striatum (TuS, also known as the olfactory tubercle) is part of both the ventral striatum and the olfactory system, which uniquely positions it to integrate both reward and odor information. Here, we examined how adolescent mice interact with e-cig odors by analyzing their odor-evoked respiration acquired in an unrestrained whole-body plethysmograph. We selected commercially available juices, including strawberry, which is commonly 'vaped' by human e-cig users. While mice investigated all stimuli through sniffing and could readily discern between stimuli, they spent more time in high frequency, investigatory sniffing when presented with the odor of strawberry or nicotine + strawberry compared to nicotine alone. These data indicate that the e-cig strawberry odor is appetitive, whether presented alone or with nicotine, and suggests that it promotes nicotine exposure. We then utilized in vivo fiber photometry and the novel dopamine (DA) sensor, GRABDA, to measure DA release in the TuS during e-cig odor presentation. Our preliminary data suggest that presentation of strawberry-containing odors elicits greater DA release in the TuS than nicotine-only odors. This work indicates that DA release in the TuS may mediate the appetitiveness of e-cig odors and points to an important role for odors in e-cig reinforcement.

W2. Oxytocin Attenuates Alcohol Consumption in a Rat Model of Oxycodone+Alcohol Polysubstance Use

Courtney Wilkinson, Isabel Leon, Lori Knackstedt*

The co-use of alcohol and opioids is common and worsens treatment outcomes, impairs successful treatment of opioid use disorder, and is involved in approximately 15% of overdoses. Oxytocin represents a potential treatment for alcohol use disorder, as it has been shown to reduce alcohol intake in preclinical models. The present study investigates whether oxytocin's effect on alcohol consumption persists in the presence of oxycodone+alcohol polysubstance use (PSU) and whether anxiety is a moderating factor. Twenty-three Sprague-Dawley rats (12 male, 11 female) were pre-screened for anxiety-like behavior using acoustic startle response (ASR) and elevated plus maze (EPM). Rats were next given access to either oxycodone (0.1 mg/mL) and water in a two-bottle choice

paradigm, or water alone, for 6 hr/day for 7 days. Subsequently rats underwent alcohol training using the intermittent access to alcohol (IAA) paradigm where rats were given access to alcohol (20% v/v) and water or water alone for five 24 hr periods, separated by 24 hr with no access. Rats were then permitted two-bottle choice access to oxycodone only (OXY, n=7), alcohol only (ALC, n=8), or both oxycodone and alcohol (PSU, n=8) for 12 days. During these 12 days, rats were given 3 hr access to oxycodone and/or water, followed by 6 hr access to alcohol or water with oxytocin (0, 0.3 or 1.0 mg/kg, IP) administered 30 minutes prior to alcohol access. Anxiety-like behavior prior to drug access predicted later oxycodone intake in both sexes and alcohol intake only in females. A prior history of oxycodone intake led to increased alcohol consumption in both sexes. Oxytocin (0.3 mg/kg) attenuated alcohol consumption in male and female PSU rats. These results highlight the role of anxiety in the motivation to voluntarily consume oxycodone and alcohol, and suggest oxytocin remains a viable treatment to decrease alcohol consumption in alcohol+oxycodone polysubstance users.

W3. Intermittent Cocaine Self-Administration in Rats Has Sex-Specific Effects on Addiction-Like Behaviors: Cue Extinction, Habitual and Compulsive Cocaine Seeking, and Motivation

Brooke Bender, Mary Torregrossa*

Intermittent access (IntA) models of cocaine self-administration, involving daily sessions of cocaine access separated by periods of cocaine unavailability, were developed to better model in rodents how cocaine is used by human drug users. Compared to traditional continuous access (ContA) models, IntA has been shown to facilitate compulsive, binge-like cocaine taking and increased motivation for cocaine. However, these experiments have been done primarily in male rats, and the effects of IntA on the efficacy of Pavlovian cue extinction or habit-like, DLS dopamine-dependent cocaine seeking have not been examined. We hypothesized that IntA would promote addiction-like behaviors, including DLS dopamine dependence and resistance to cue extinction. Male and female rats were implanted with jugular vein catheters and DLS cannula and trained to self-administer cocaine paired with an audiovisual cue on a ContA or IntA schedule. In subsets of rats, the role of Pavlovian audiovisual cues on drug seeking was tested with a 120-cue or 0-cue control procedure followed by a cue-induced drug-seeking test; motivation for cocaine was tested using a progressive ratio procedure; compulsive cocaine taking was tested by pairing cocaine infusions with footshocks; and dependence of behavior on DLS dopamine (a measure of habit-like behavior) was tested by examining the effects of DLS infusion of the dopamine antagonist flupenthixol. Overall, cue extinction reduced cue-induced drug seeking after ContA or IntA. Compared to ContA, IntA resulted in increased motivation for cocaine in males and females. IntA facilitated more compulsive cocaine taking exclusively in males. After moderate (10-11 days) IntA training, DLS infusion of dopamine antagonist reduced cue-induced drug seeking. Novel findings indicate that moderate (10-11 days) IntA promotes DLS dopamine-dependent, habit-like drug seeking in a males and females and promotes compulsive cocaine taking primarily in males.

W4. Behavioral Disturbances of Emotionality and Alcohol Drinking as a Result of Low Social Rank in C57BL/6J Mice

*Nick Ahmed, Alisha Hoefs, Lara Hwa**

As many socioeconomic variables impact the human outcomes of stress, mood, and substance use disorders, this research seeks to identify the underlying stress neurobiology of social hierarchy in animal models. Mammalian social rank has been used to compare social dominance versus subordination to gain access to social stress-related brain circuits. To create and measure behavioral outcomes of a self-organized social hierarchy, male and female C57BL/6J mice are group-housed before social dominance testing using the tube test and a battery of stress-related behavioral assays are performed. Specific assays include the open field, elevated plus maze, three-chamber social interaction test, exposure to predator odor, forced swim test, and intermittent, two-bottle choice alcohol drinking. Our preliminary data show lower-ranked male mice consume greater levels of alcohol compared to their higher-ranked cage mates. It is predicted that lower-ranked male mice will exhibit behavioral phenotypes similar to chronic stress models in tests of anhedonic-like behavior and stress responding, but this may be different in female mice. One known biomarker of chronic stress susceptibility is the neuropeptide corticotropin-releasing factor (CRF) and its influence on serotonin pathways in the brain. Sites such as the medial prefrontal cortex (mPFC) and dorsal raphe nucleus (DRN) have been linked to formation of a social hierarchy and stress coping. Our future studies use will CRF-specific electrophysiology and fiber photometry in CRF-containing neurons to measure social hierarchy-induced stress signaling in the mPFC and DRN. These methods allow for the characterization of CRF neurons using synaptic transmission and in real-time behavioral responding to stress to compare low versus high social rank. These experiments study the neurobiological adaptations that impact social hierarchy formation to begin to understand the complex variables of human chronic stress.

W5. Cell-Type Specific FGF13 Regulation of Cortical Function

Susan Lin, Aravind Gade, Honggang Wang, Isabella Distefano, Anjali Rajadhyaksha, Geoffrey Pitt*

Fibroblast growth factor homologous factor 13 (FGF13) is a non-canonical member of the fibroblast growth factor (FGF) superfamily that is not a secreted growth factor and functions intracellularly. Long-studied for its role in regulating voltage-gated sodium channels in brain and heart, the full complement of FGF13 molecular functions is undefined. Clinical studies revealed that patients with disruptions or mutations in the Fgf13 gene have early onset cognitive impairment and febrile seizures. FGF13 has two major alternatively-spliced isoforms in the cerebral cortex, one which is predominantly expressed in excitatory and the other in inhibitory cells. To study cell-type specific FGF13 expression, I generated mice lacking FGF13 throughout CamkIIα-expressing glutamatergic or Gad2-expressing GABAergic interneurons. Mice heterozygous for Fgf13 in interneurons suffer epileptic seizures, consistent with the human phenotype, and hemizygous knockout mice die perinatally. Mice with Fgf13 deficiency in glutamatergic cells survive through adulthood. To further define the functional roles of FGF13, I conducted a battery of behavior assays to identify differences between knockout mice and wildtype littermates. My findings reveal cell type specific roles of Fgf13 in cocaine

contextual memory, likely mediated by distinct molecular mechanisms. These data show that differential regulation of Fgf13 via alternative splicing generates distinct proteins with different neuronal functions.

W6. Isoform-Selective PI3-Kinase Inhibition Confers Partial Resilience to Cocaine Cessation-Induced Anxiety-Like Behavior

Britton Barbee, Shannon Gourley*

Phosphoinositide 3-kinase (PI3K) is a multi-subunit signaling complex that phosphorylates phosphoinositides, membrane-embedded second messengers that are critical for synaptic and structural plasticity of neurons. Cocaine potentiates PI3K-Akt-mTOR cascade activity, and this activation persists beyond the period of drug exposure. The PI3K p110β isoform is neuronally enriched and able to control PI3K signal propagation, allowing for manipulation of PI3K activity in a more targeted manner than broad-spectrum PI3K inhibition. Cessation of cocaine use triggers anxiety-like behavior in humans and rodent models, and anxiety can be a causal factor in relapse. Here, we used viral-mediated gene silencing to reduce expression of p110β in the dorsomedial prefrontal cortex (dmPFC). Isoform-selective PI3K inhibition mitigated anxiety-like behavior triggered by acute cocaine. Interestingly, however, a history of repeated cocaine exposure occluded this resilience, presenting an opportunity to compare immediate-early gene expression between cocaine-vulnerable and cocaine-resilient mice. We examined 22 brain regions and found that resilient mice – those displaying less anxiety-like behavior – displayed lower immediate-early gene expression in the claustrum and lateral hypothalamus. We next found that chemogenetic stimulation of the claustrum induced anxiety-like behavior. Future studies will determine whether suppressing p110β in the dmPFC combats anxiety-like behavior via connections with the claustrum. Our findings suggest that isoform-selective PI3K inhibition mitigates cocaine cessation-elicited anxiety-like behavior, likely via coordinated brain regions and circuits.

W7. Mitochondrial Gene Ontology Pathways and Transcriptional Regulators Impacted by Cocaine Self-Administration in C57Bl/6 Mice

Cali Calarco, Swarnapali Keppetipola, Michel Engeln, Mary Kay Lobo*

Exposure to illicit drugs and subsequent chronic use profoundly impacts behavior, neuronal structure and firing, and gene expression through multiple brain regions. Some of these sweeping changes are mediated by and supported by changes in cellular energy homeostasis and mitochondrial function. Recent work has shown that cocaine self-administration significantly alters mitochondrial size in nucleus accumbens medium spiny neurons, and that disruption of proper mitochondrial fission is sufficient to blunt responding for cocaine. Beyond mitochondrial fission, other aspects of the mitochondrial energy cycle are impacted by cocaine exposure. At the transcriptional level, many genes altered by cocaine self-administration are related to cellular metabolism and mitochondrial function. In this study we conducted gene ontology analysis on an RNA-seq data set generated from mice that had undergone cocaine self-administration, with a focus on mitochondrial-related ontology terms. The sequencing data set included tissue from the prefrontal cortex, nucleus accumbens, dorsal striatum, ventral pallidum, amygdala,

hippocampus, and ventral tegmental area. We found significant representation of transcriptionally regulated genes in metabolism and mitochondrial related gene ontology terms in multiple brain regions. Further, predictive analysis of transcription factor regulation of identified mitochondrial-related genes identified a number of transcription factors across brain regions that may control cocaine-related changes in mitochondrial function. Future work will be needed to validate these predicted targets in vivo and understand their role in regulating the cellular and behavioral responses to cocaine self-administration.

W8. Transcription Factor 4 Coordinates Gene Expression and Dopamine Responses in the Nucleus Accumbens

Nathaniel Robinson, Jenna Hinds, Saige Thompson, Kendra Bunner, Jeremy Day*

Substance use disorders are an increasingly common cause of morbidity and mortality, owing in part to an incomplete understanding of the molecular mechanisms that drive behavioral responses to drugs of abuse. Psychostimulants, such as cocaine, exert their effects through maladaptive enhancement of dopamine (DA) neurotransmission in the reward circuitry, particularly the nucleus accumbens (NAc). Within the NAc, these drugs promote DA-dependent transcriptional and epigenetic alterations in medium spiny neurons (MSNs) that are governed by master transcription factors (TFs). However, a comprehensive understanding of the epigenetic mechanisms that orchestrate drug-induced DA responses remains elusive. Our work has identified transcription factor 4 (TCF4) as a putative effector of DA-mediated transcriptional reprogramming in the NAc. TCF4 has been previously implicated in neurodevelopment and neuropsychiatric disease, but its functions in the reward circuitry are unknown. Mechanistically, TCF4 regulates a transcriptional network that includes genes involved in DA signaling and synaptic plasticity. In line with this, modulation of TCF4 in MSNs using a novel CRISPR activation and inhibition strategy bidirectionally alters DA-induced gene expression and neuronal activation. Moreover, TCF4 is differentially expressed in the NAc following repeated cocaine administration. Collectively, our results reveal a previously unknown function for TCF4 in coordinating DA signaling and gene expression in a key brain reward structure that is targeted by cocaine. These findings expand our knowledge of the epigenetic landscape of psychostimulant action and provide a foundation for examining the contributions of TCF4-mediated gene expression programs to addiction-related behaviors.

W9. Investigating the Redox Regulation of Histone Deacetylase 5 in Cocaine-Seeking Behavior

Daniel Wood, Taniguchi Makoto, Susana Comte-Walters, Lauren Ball, Evgeny Tsvetkov, Christopher Cowan*

Substance Use Disorder is a chronic, relapsing behavioral disorder characterized by compulsive drug seeking and use despite adverse consequences to the individual. Repeated drug use causes persistent neuroadaptations in the nucleus accumbens (NAc), a brain region associated with reward and motivation. In abstinent drug users, relapse can be triggered by drug-associated environmental cues long after drug-cessation. Although the

molecular mechanisms underlying relapse are not fully understood, epigenetic regulation of gene expression is an important process involved in the lasting association between reinforced behavior and drug-associated cues. Our lab has previously shown that the epigenetic enzyme, histone deacetylase 5 (HDAC5), functions in the NAc as a critical negative regulator of relapse-related behavior in rodents. HDAC5 is an activity-regulated enzyme that shuttles between the cytoplasm and the nucleus, where it functions to repress associated gene transcription. Evidence in the literature suggests HDAC5's effects on transcription may be regulated by drugs of abuse through the oxidation of two conserved cysteines within HDAC5's enzymatic domain. Here we show that these cysteines form a disulfide bond in vitro and mutation of these cysteines may disrupt HDAC5's ability to reduce cue-induced reinstatement of cocaine-seeking following cocaine self-administration. This mutation also blocks HDAC5's ability to reduce intrinsic excitability of NAc medium spiny neurons. Interestingly, we observe no changes in subcellular localization of this mutant or its ability to repress MEF-dependent transcription, suggesting alternative mechanisms are responsible for the observed behavioral and electrophysiological changes. Together, our data point toward a critical role of these conserved cysteines in HDAC5's anti-relapse actions and suggest that they may be redox-sensitive. Future studies will investigate the role of these cysteines in intrinsic HDAC5 enzymatic function and in binding of co-repressors, as well as the in vivo redox regulation of these cysteines by cocaine exposure.

W10. Gabaergic and Glutamatergic Ventral Pallidum Neurons Differentially Encode Motivation for Heroin

Nicholas Fayette, Brandi Wiedmeyer, Jasper Heinsbroek*

Opioid use disorder (OUD) and associated overdose deaths are still on the rise worldwide. Effective treatment strategies for OUD are lacking due to an incomplete understanding of the neural circuit mechanisms that mediate opioid use. The ventral pallidum (VP) is a central node in the ventral basal ganglia circuits that drive relapse, and contains GABAergic and glutamatergic neurons that oppositely encode motivated states. Here we used miniscope calcium imaging in mice that were chronically implanted with gradient index lenses above the VP to study the roles of these populations during heroin use. We observed that GABA neurons show more pronounced activation around nose pokes for heroin than glutamate neurons. By contrast, glutamatergic neurons had increased tonic activation as measured by calcium event frequency. Finally, when mice were subjected to unpredictable reward conditions (a variable ratio schedule of reinforcement), GABA but not glutamate neurons significantly increased their tonic activation. Collectively, these data demonstrate that GABA neurons in the VP more potently encode the motivation to use heroin in mice.

W11. Bidirectional Relationship Between Opioids and Disrupted Sleep

Darrell Eacret, Julia Noreck, Crystal Lemchi, Polina Fenik, Sigrid Veasey, Julie Blendy*

Opioid use disorders (OUDs) constitute a major public health burden. One adverse effect of opioid use and withdrawal is disrupted sleep, and poor sleep increases one's risk of drug use. Individuals with an OUD have poorer sleep and increased sleep fragmentation compared with healthy adults, and even report sleep disturbances during withdrawal as a reason for relapse. However, studies examining how sleep is affected by opioid use/withdrawal, and how poor sleep influences vulnerability to opioid use are lacking. To investigate this in a more tractable system, we implanted mice with EEG/EMG electrodes during an oral morphine exposure protocol and found mice stay awake more and spend less time asleep during the active period. Removal of morphine increases wake and decreases NREM during the inactive period. This increased wake during morphine is accompanied by a gene expression profile similar to an inflammatory sleep disrupted state and produced affective behavior deficits following a 2-week abstinence period. In addition, this chronic oral morphine exposure paradigm is associated with increased cFOS activity in the paraventricular nucleus of the thalamus (PVT) following acute and chronic morphine exposure. To determine whether cells in the PVT are required for morphine-induced wakefulness, we injected a cre-dependent inhibitory DREADDs virus into the PVT to specifically silence mu opioid receptor expressing cells. To examine the bidirectional influence of sleep and opioids, we sleep deprived mice and saw no preference in a morphine 2 bottle choice test, while controls did show a morphine preference. We are currently repeating the sleep deprivation study with morphine conditioned place preference to distinguish whether this phenotype is due to a lack of rewarding properties of morphine or due to a lower dose of morphine being sufficient for reward. Overall, these studies should contribute to finding the mechanism underlying the relationship between opioids and sleep.

W12. Knock Down of Irf8 in Brain Using an ASO Protects Against Synapse Loss in a Mouse Model of HIV Associated Neurocognitive Disorder

Fredrik Kamme, Christine Hong, Hina Singh, Ricky Muang, Marcus Kaul*

Chronic neuroinflammation in HIV+ patients is believed to contribute to HIV Associated Neurocognitive Disorder, characterized by cognitive-, memory- and mild motor-impairment. Previous work has demonstrated significant microglial and astrocytic responses in a transgenic mouse model expressing HIV gp120. Genetic ablation of CCR5 in the same model prevented microglial activation and protected against synapse loss, pointing to a central role of microglia and neuroinflammation in the disease.
Irf8 is a key myeloid transcription factor, playing roles in development and inducible IFN signaling. In the brain, only microglia express Irf8. We developed ASOs against mouse Irf8 to pharmacologically modulate microglia in vivo and used them in the HIV gp120 transgenic mouse model of HAND. Tissues were analyzed for synapse density by immunofluorescence and deconvolution microscopy. The effect of Irf8 knockdown on

microglia was assessed by microglia isolation and RNA profiling using DGE.

Results show protection against synapse loss by Irf8 knock down. Interestingly, delayed treatment recovered synapses already lost, suggesting lost functions can be recovered upon therapy.

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W13. Prefrontal Dopamine Interferes With the Protective Effects of Behavioral Control in Females

Connor McNulty, Isabella Fallon, Jose Amat, Nathan Leslie, Rory Sanchez, Linda Watkins, Steve Maier, Michael Baratta*

Instrumental control over stress blunts many of the neurochemical and behavioral outcomes that typically follow exposure to physically identical uncontrollable stress. Current evidence indicates that the stress-buffering effects of behavioral control require engagement of a corticostriatal circuit, involving the prelimbic cortex (PL) and dorsomedial striatum (DMS). Interestingly, the protective effects of control are completely absent in females. Here we demonstrate that female rats acquire the controlling response through a PL independent dorsolateral striatal (DLS) system. Following intra-DLS excitotoxic lesions, control over stress now provided protection in females. Furthermore, behavioral control potently reduced prefrontal dopamine levels in males but had no effect in females, in which dopamine remained elevated. Subsequent fluorescent in situ hybridization revealed that PL GABA interneurons preferentially express the D1 receptor subtypes, independent of sex. Intra-PL infusions of the D1 antagonist SCH-23390 (0.5µl / hemisphere) now led control to be protective in females. In addition, PL D1 antagonism enhanced activation within the dorsal medial striatum. These findings suggest that the protection depends upon the learning system used rather than coping per se. Furthermore, reduced benefit from a resilience factor may present a novel approach to understanding sex differences in stress-linked psychiatric disorders.

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W14. The Role of Prefrontal-Periaqueductal Gray (PAG) Circuits in Conditioned Fear

Julia Mitchell, Leilani Potgieter, Leena Ziane, Lauren Huslhof, Rebecca Shansky*

The dorsal and ventral periaqueductal gray (d/vPAG) play roles in active and passive threat responses, respectively. They receive input from the infralimbic cortex on a rostral/caudal gradient (r/cIL): rIL-vPAG and cIL-dPAG. Activation of the cIL-dPAG circuit could increase an animal's likelihood to engage in active threat responses, such as darting. Darting is a sex-dependent conditioned fear response characterized by a quick movement across a fear conditioning chamber in response to a conditioned stimulus (CS). Forty percent of females dart while only ten percent of males do. Darters also reach higher shock and post-shock velocities compared to non-darters. In this study we tested the hypothesis that excitation of the cIL-dPAG pathway would increase the number of darters across the sexes using an intersectional, excitatory DREADDs approach. We injected a

cre-dependent, excitatory Gq (or control) virus into the cIL, and a retrograde-cre virus into the dPAG. After 6 weeks all animals received an injection of clozapine-n-oxide (CNO) to activate the cIL-dPAG circuit before undergoing classic Pavlovian Fear Conditioning. Using ScaredyRat, a custom Python tool designed in our lab to analyze raw Ethovision Data files, we quantified the number of darters and the animals' shock and post shock velocities. Although we did not see an increase in darters, we observed a significant decrease in freezing for Gq females compared to controls. There was no difference between Gq males and their control group, and no difference in shock and post-shock response between groups in either females or males. These data indicate that excitation of the cIL-dPAG circuit, although not apparently involved in darting, might influence an animals' propensity to freeze in response to a CS in a sex-dependent manner. Future studies are investigating the organization of projections from the IL to the dPAG and vPAG in both males and females, as well as pain's possible role in conditioned fear responses.

W15. Nucleus Accumbens Neuron Subtype Translatomes in Social Stressed Females

Gautam Kumar, Daniela Franco, Megan Fox, Basu Mahasweta, Jimmy Olusakin, Makeda Turner, Seth Ament, Mary Kay Lobo*

Stress can impact vulnerability for mental illness including depression. While depression occurs in both sexes there is a higher prevalence in females. However, social stress paradigms in animals often include only male subjects. To overcome this limitation, we used the chronic witness social defeat stress (CWDS) in female subjects. We employed a social preference test with same sex conspecifics to demonstrate a susceptible group that displays reduced social preference and a resilient group with social preference similar to controls. To elucidate the molecular mechanisms that underlie these individual differences in females exposed to CWDS we employed translatome RNA-seq profiling in nucleus accumbens (NAc) projection neuron subtypes, the dopamine receptors D1- and D2-expressing medium spiny neurons (D1-MSNs and D2-MSNs). Weighted gene coexpression analysis (WGCNA) identified gene network modules significantly regulated by stress in MSN subtypes, with both stress susceptible and resilient regulated modules in D1-MSNs and only stress susceptible regulated modules in D2-MSNs. Further analysis of the WGCNA modules revealed that more modules for the D1-MSNs are regulated in resilient mice and represent molecules involved in development and proliferation, mitochondrial activity and immune responses. D2-MSN susceptible modules are enriched in molecules involved in transcription, metabolic processes, and synaptic processes. Consensus modules covering both D1- and D2-MSNs were also identified. Consensus modules involved in transcriptional regulation and protein processing were shown to be downregulated in the stress susceptible group while consensus modules involved in synaptic structures were upregulated. Collectively, our studies uncover altered molecular processes in NAc neuron subtypes that may underlie female stress response.

W16. Impact of Social Defeat Stress on Microglia-Neuron Interactions in the Nucleus Accumbens

Daniela Franco, Benjamin Siemsen, Megan Fox, Mary Kay Lobo*

Exposure to chronic stress in mice, a known risk factor for depression, produces long-lasting changes to the nucleus accumbens (NAc). Specifically, dendritic atrophy of dopamine receptor type 1 (D1)-, but not D2,-expressing medium spiny neurons (MSNs) is necessary for chronic stress-induced depressive-like behavior. Here, we hypothesized that D1 dendritic atrophy would be associated with increased contact of D1-MSNs by microglia processes, facilitating dendritic retraction. Male D1-CX3CR1-GFP and D2-CX3CR1-GFP mice were subjected to 10 days of Chronic Social Defeat Stress (CSDS), during which subjects were directly socially defeated by a male aggressor. This model produces cohorts that are either susceptible or resilient to CSDS-induced depression-like behavior. Unstressed littermates were used as controls. 3D reconstruction analyses of D1 or D2 MSNs and adjacent microglia in the NAc were performed on confocal Z-stacks to quantify microglia morphology and contact at MSNs. We found that CSDS reduced the overall microglia contact at D1, but not D2, MSNs, but that the degree to which microglia contact MSNs in stressed animals negatively predicted CSDS-induced decreases in social interaction. That is, animals displaying the greatest social avoidance showed the greatest microglia-D1 MSN contact. Interestingly, CSDS decreased the microglia density in the area occupied by D1 MSN dendrites, yet the average volume of microglia somas (an index of activated microglia) in this region was increased by CSDS, which also negatively predicted CSDS-induced social avoidance. Finally, reconstruction analyses of individual microglia within the region occupied by D1 MSNs revealed that animals susceptible, but not resilient, to CSDS displayed reduced microglia complexity. Overall, these results add to the growing body of literature implicating microglia in maladaptive disease states, and future studies will focus on causally linking microglia alterations to anhedonia.

W17. Repetitive Transcranial Magnetic Stimulation (rTMS) Treatment With Concurrent Measurement of Salivary Biomarkers in Major Depressive Disorder

Ronald See, Branon Eusebio, David Agnew, Mark Heatwole*

Steroid hormones may serve as potential biomarkers of treatment response for major depressive disorder (MDD). Here, we assessed salivary levels of cortisol, dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEA-S), as well as alpha amylase activity, across 30 sessions of bilateral repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex in MDD patients. While rTMS significantly improved symptoms as measured by three different symptom scales, salivary biomarker levels and their ratios showed no significant changes across sessions. These results do not support the routine clinical use of these biomarkers as reliable indicators of treatment outcome during rTMS administration for MDD.

W18. Molecular Profiling of the Hippocampus in Children With Autism Spectrum Disorders

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Several lines of evidence point to a key role of the hippocampus in Autism Spectrum Disorders (ASD). Altered hippocampal volume and deficits in memory for person and emotion related stimuli have been reported, along with enhanced ability for declarative memories. Preclinical models have demonstrated a critical role of the hippocampus in social memory dysfunction, associated with ASD, together with decreased synaptic plasticity. There is a lack of information regarding the molecular pathology of the hippocampus in children with ASD. We used RNAseq profiling on postmortem human brain samples containing the hippocampus from children with ASD (n=7) and normal children (3-14 yrs old), (n=7) from the NIH NeuroBiobank to test the hypothesis that molecular pathways are altered in the developing hippocampus of children with ASD. QRT-PCR was used to confirm differentially expressed genes. RNAseq analysis implicated molecular pathways involved in neurodevelopment, extracellular matrix organization, synaptic regulation, L-type calcium channel signaling, and inflammatory response. Extracellular matrix molecules (ECMs) and MEF2C are critically involved in regulating neurodevelopment, synaptic plasticity, and immune system signaling, representing key links between these systems. We further examined these relationships with Western Blotting and microscopy analysis. Protein expression of inflammatory molecules (IL-1ß and IBA1), the ECM protease MMP9, synaptic markers (PSD95 and SYN1), and MEF2C were examined in the same cohort. We observed decreased expression of synaptic proteins PSD95 ($p<0.02$) and SYN1 ($p<0.02$), along with decreased expression of MEF2C ($p<0.03$). We also observed increased expression of the pro-inflammatory protein IL-1ß ($p<0.04$) and the ECM protease MMP9 ($p<0.03$). Immunofluorescence microscopy analysis revealed increased BCAN expression in GFAP positive astrocytes in children with ASD, together with altered astrocyte morphology. Our results point to altered inflammatory response, glia cell differentiation, and synaptic dysfunction in the hippocampus of children with ASD, together with broad alterations in ECM molecules. Furthermore, our results implicate molecular pathways involved with several genetic factors associated with ASD including ECM molecules and MEF2C.

W19. Multisensory Predictive Coding in Rodent Posterior Parietal Cortex

Alice Van Derveer, Connor Gallimore, Jordan Hamm*

In a predictive coding framework, the brain is believed to generate predictive models which affect information processing at each stage in a hierarchically organized cortical network. Incoming sensory information is compared against these models, suppressing neural responses to expected stimuli and augmenting responses to unexpected stimuli. This modulation is evident in primary sensory cortices during a basic unisensory oddball paradigm; neural activity is reduced to repetitive stimuli (stimulus specific adaptation;

SSA) and augmented to deviant stimuli (deviance detection; DD). It is unknown whether this occurs in higher-order regions of cortex, such as posterior parietal cortex (PPC), a critical region for multisensory (MS) integration. Mouse PPC exhibits strong SSA, yet little DD to unisensory (US) stimuli. We hypothesized that PPC exhibits DD to complex MS stimuli. We measured neuronal activity in PPC with two-photon calcium imaging in awake mice. For the US visual "oddball" paradigm, we presented 8 full square-wave gratings drifting in a random order (many standards control), then an oddball sequence with one redundant grating (88% "standards") and one deviant grating (12% "oddballs"). For the US auditory "oddball" paradigm, we presented mice with 8 auditory frequencies in a random order, then an oddball sequence with one redundant tone (88% "standards") and one deviant tone (12%"oddballs"). Responses to the same stimulus were compared between oddball and many standards contexts to assess US DD (n=10, male and female). For the MS paradigm, visual (45º [Va] and 135º [Vb]) and auditory stimuli (2.0kHz [Aa] and 4.0kHz [Ab]) were paired and presented semi-simultaneously (<10ms delay). Mice were trained with sequences of AaVa and AbVb combinations, then presented MS "oddball" sequences, consisting of 87.5% trained pairs and 12.5% deviant pairs. Responses to control and deviant MS pairs stimuli were compared (n=6, male and female) to assess MS DD. Robust MS DD ($t(120)=4.29$, $p<.0001$), but not US DD (auditory: $t(318)=0.87$, $p=.385$; visual: $t(311)=0.56$, $p=.575$), was observed at the population level. These results suggest that while simple US prediction errors do not propagate through the cortical hierarchy to PPC, prediction errors to novel MS combinations generate genuine DD in PPC.

W20. Schema Cells in Orbitofrontal Cortex

Wenhui Zong, Jingfeng Zhou, Matthew P. H. Gardner, Geoffrey Schoenbaum*

Previous studies have consistently supported the idea that the orbitofrontal cortex (OFC) contributes to cognitive mapping, and we have recently shown that neural activity in the OFC converges on a generalized cognitive map – a schema – when trained repeatedly on exemplars of a complex, 24-position, odor sequence task (Zhou et al, Nature, 2021). To further explore the representations of schemas in OFC, we repeated this study, using a much-simplified version of this task in which ten different odors were arranged in two "virtual" figure 8 mazes. The shape of the two mazes was identical however each used unique odors. Neurons were recorded during performance on each maze, and we hypothesized that schema representations would be characterized by similar firing patterns between the two mazes. Consistent with this, we found that while aspects of the individual mazes were represented by some neurons (odor, odor sequence, reward), many OFC neurons exhibited highly correlated firing patterns across mazes, consistent with extraction of the generalized cognitive map. We will present these results, and if feasible we hope to show data from ongoing work examining how these encoding features evolve during learning and the impact of inactivation of hippocampal regions classically responsible for cognitive mapping.

W21. Dissociating Dopaminergic and Subthalamic Contributions to Effort-Based Decision Making

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. This mechanism has been interpreted in terms of an informational lesion in the STN induced by DBS. The effects of DBS contrast with the effects of dopaminergic medication (which alter the weighting of benefits vs costs of decisions), though both mechanisms could account for increased impulsive behavior. Here we evaluate whether low vs high frequency (4 hz vs. 130 hz) stimulation in different STN contact locations (dorsal vs ventral) can have differential effects on decision threshold and/or cost-benefit decision making in a physical effort-discounting task using a within-subject design. We present behavioral data and a computational characterization of DBS' effects on cost/benefit decision making collected from STN DBS PD patients and age matched controls. Behavioral analysis confirms patients make stable choices relative to their indifference point. Furthermore, computational modeling captures DBS and dopaminergic effects due to subsequent changes in cost/benefit drift rate and threshold parameters. Specifically, these computational results are captured via the differential slopes of patients' psychometric functions. Preliminary analysis indicates there's an interaction between DBS condition (specifically 4hz ventral DBS stimulation) and dopaminergic status on patients' choices and response times.

W22. Learning Task Structures in Reinforcement Learning through Hierarchical Clustering

Rex Liu, Michael Frank*

A hallmark of human intelligence is our ability to compositionally generalize: that is, to recompose familiar knowledge components in novel ways to solve new problems. For instance, a talented musician can conceivably transfer her knowledge of flute fingerings (transition functions) and guitar songs (goals) to play guitar music on a piccolo for the first time. Yet there are also instances where it can be helpful to learn and transfer not just individual task components, but entire structures or substructures, particularly whenever these recur in natural tasks (e.g., in bluegrass music one might transfer the joint structure of finger movements and musical scales from one stringed instrument to another). Prior theoretical work has explored how agents can learn and generalize task components or entire latent structures, but a satisfactory account for how a single agent can simultaneously satisfy the two competing demands is still lacking. Here, we propose a hierarchical model-based agent that learns and transfers individual task components as well as entire structures by inferring both through a non-parametric Bayesian model of the task. It maintains a factorised representation of task components through a hierarchical Dirichlet process, but it also represents different possible covariances between these components through a standard Dirichlet process. We validate our approach on a variety of navigation tasks covering a wide range of statistical correlations between task components

and show that this hierarchical framework can also be applied to improve generalisation and transfer in hierarchical tasks with goal/subgoal structures. Finally, we discuss how this clustering algorithm could conceivably be implemented by cortico-striatal gating circuits in the brain.

W23. Anterior Cingulate Neurons Signal Valueless Associative Information During Sensory Preconditioning

Evan Hart, Matthew Gardner, Geoffrey Schoenbaum*

Anterior cingulate cortex (ACC) signals myriad items with clear biological significance. Recording studies in rats, humans, and other primates have reported diverse neural responses that support many theories of ACC function. Yet nearly all these studies have in common tasks in which one event reliably predicts another. This leaves open the possibility that ACC simply represents associative pairing of events, independent of their biological significance. To test whether this is the case, we recorded single neurons in ACC during a sensory preconditioning task in which rats initially learned to associate two biologically neutral cues. ACC neurons developed firing patterns that reflected the learning of these sensory associations, even though no biologically significant reward was present. The strength of these neural correlates predicted rats' ability to later mobilize and use that associative information after the second cue had been paired with reward. These results demonstrate that biological significance is not necessary to produce correlates of learning in ACC.

W24. Gabaergic and Glycinergic Synaptic Transmission in Respiratory-Controlling Kölliker-Fuse Neurons in Female and Male Rett Syndrome Mice

Jessica Whitaker-Fornek, Erica Levitt*

Rett Syndrome (RTT) is a neurodevelopmental disorder characterized by severe motor behavior disturbances including breathing problems. RTT is caused by silencing mutations in the methyl-CpG binding protein 2 (MeCP2) gene located on the X chromosome. Accordingly, girls and women account for the majority of RTT patients. The genetic nature of RTT lends itself to study in mice with loss of function mutations in the MeCP2 gene. Importantly, RTT mice display breathing irregularities similar to human patients. Insufficient inhibitory neurotransmission in the brainstem respiratory network is thought to contribute to the breathing problems in RTT. In the pontine Kölliker-Fuse (KF) area of RTT mice, there are fewer GABAergic axon terminals and injection of a GABA reuptake antagonist alleviates breathing problems in vivo. However, no one has examined the physiology of GABA or glycine synapses in the KF of RTT mice. In the present work, we tested the hypothesis that GABAergic and glycinergic synapses are deficient in the KF of RTT mice. We performed whole-cell voltage clamp recordings from KF neurons contained in brain slices of MeCP2-deficient RTT mice and wild type littermates. The frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) in the KF neurons of male RTT mice was reduced compared to WT littermates. In contrast, female RTT mice showed no change in sIPSC frequency in the KF compared to control, despite having breathing abnormalities. The amplitude of sIPSCs in the KF of female mice were smaller compared to WT littermates, whereas male RTT mice showed no change in amplitude compared to

WT littermates. These results spotlight the importance of studying respiratory controlling KF neurons in both male and female RTT mice, and suggest that reductions in IPSC frequency and amplitude are not sufficient to explain the breathing irregularities observed in RTT in females and males, respectively.

W25. Development of Medial Prefrontal Cortex Circuitry and its Role in the Maturation of Adaptive Avoidance in Mice

Caitlin Goodpaster, Cassandra Klune, Rita Chen, Laura DeNardo*

The medial prefrontal cortex (mPFC) and its circuitry regulates numerous adaptive functions in both humans and rodents, including decision making. Many mPFC-dependent behaviors mature from adolescence to adulthood, which may reflect the protracted developmental period of mPFC. Despite the critical control that mPFC exerts over behavioral functions, when specific mPFC circuits mature and how they regulate behavior across development is poorly understood. This study aims to define developmental changes of mPFC projections to the nucleus accumbens (NAc) and basolateral amygdala (BLA) and their contribution to adaptive avoidance behavior from the postnatal period to adulthood in mice. We utilized an adapted platform mediated avoidance (PMA) task in which a fear conditioned tone prompts rodents to navigate to a safety platform. PMA has previously shown to be
bidirectionally modulated by mPFC projections to NAc and BLA in rats. We found that PMA behavior is developmentally regulated. Postnatal day (P)23, P28, P35, and adult mice all learned to avoid the shock within a single training session. However, during a retrieval session 24 hours later, stark age differences emerged. P28 and adult mice spent about 80% of the time during the tone on the platform, suggesting retention of the learned avoidance response. However, P23 and P35 mice spent significant less time on the platform suggesting age-dependent differences in behavioral strategy or retention deficits. Optogenetic manipulations of mPFCàNAc and mPFCàBLA neurons during PMA produced age dependent effects. Further, fiber photometry experiments showed that NAc and BLA show differential response dynamics during PMA at P23, P35 and in adulthood. These finding suggest that developmental changes in mPFC circuits to BLA and NAc may regulate the maturation of avoidance behavior. Understanding how mPFC circuits develop in the typical brain is foundational to how their development may be perturbed and contribute to disease states.

W26. Simultaneous Real-Time Detection of Multiple Neurochemicals at Single Recording Sites Using Carbon-Fiber Microbiosensors Coupled With Voltammetry

Leslie Sombers, John Meitzen, Alexandra Forderhase, Jack Twiddy, Laney Kimble*

Striatal dopamine signaling is intensely studied because it has been implicated in regulating motor control and the response to both rewarding and aversive stimuli. However, dopamine is just one voice in a cacophony of signaling molecules that work together to modulate striatal function, and the second-by-second dynamics of many other

important molecules remain largely unexplored. In this work, we describe how carbon-fiber microelectrodes can be modified with specific oxidase enzymes to create sensitive and selective microbiosensors for a variety of non-electroactive targets, including glucose, lactate, and glutamate. When coupled with fast-scan cyclic voltammetry, these biosensors can be used to monitor each of these species in rat striatum, while simultaneously monitoring dopamine fluctuations at the same recording site(s) in real time. The biosensors have been characterized for their stability, selectivity, and sensitivity to each of the target species; and simultaneous monitoring of multiple species has been demonstrated in live striatal tissue. These studies are important for many reasons, but perhaps most important because extracellular concentrations of glucose, lactate, and glutamate within the central nervous system are all tightly regulated by astrocytes. These (generally understudied) cells transport glucose, lactate, and glutamate to/from the extracellular space over the course of seconds. However, many details regarding the shuffle of these substrates between neurons and astrocytes remain ambiguous, due to a lack of analytical strategies for monitoring rapid neurochemical fluctuations on this time scale. Overall, the technology described advances the state of the art for biosensing from measurements of a single species to real-time monitoring of multiple species at a single recording site. This advance opens a world of new studies, particularly when investigating the role of astrocytes in tuning striatal function.

chemogenetics effectively rescued social behaviors in aged mutant mice. These results demonstrate that prefrontal hypoexcitability mediates FTD-associated sociability deficits and, most importantly, can be rescued even at a late disease stage when significant neural degeneration has occurred. Thus, targeted restoration of prefrontal cortex excitability could serve as a promising therapy for treating late-stage C9ORF72-associated FTD.

W28. Changes in Locus Coeruleus Firing Suggest Neuronal Hyperactivity and Coincide with Anxiety-Like Behaviors in Young TGF344-AD Rats

Michael Kelberman, David Weinshenker*

Hyperphosphorylated tau pathology, a hallmark of Alzheimer's disease (AD), appears first in the noradrenergic locus coeruleus (LC). Emergence of prodromal symptoms parallels accumulation of hyperphosphorylated tau in the LC, and are consistent with altered LC activity. In rodents, the LC also exhibits compensatory mechanisms to maintain normal function, such as lesion-induced increased firing rate of surviving neurons. How tau alters LC firing rates, whether AD-like pathology triggers compensatory mechanisms, and how these changes influence behavior is unknown. 6- and 15-month TgF344-AD rats, which overexpress AD-causing human APP and PS1 mutations and develop early endogenous tau pathology in the LC, and wild-type (WT) littermates were used for these experiments. Baseline and evoked activity of LC units were recorded. A separate group of age matched rats were tested on the elevated plus maze (EPM), open field (OF), and novelty suppressed feeding (NSF) to assess anxiety-like phenotypes. LC neurons from TgF344-AD rats exhibited lower basal firing rates compared to WT littermates. Significantly higher mid-phase responses were noted in 6-month TgF344-AD rats compared to age matched WT littermates only during 5ms 10mA footshocks. Trends towards increased footpinch-induced LC activity, elevated signal-to-noise ratio, and shorter interspike interval were also apparent in 6-month TgF344-AD rats, but were not significant. We saw no differences in anxiety-like phenotypes in the EPM or OF, but TgF344-AD rats at both ages took longer to eat during NSF. These results suggest potential compensatory mechanisms to maintain normal LC function in the presence of AD-like neuropathology that may have deleterious behavioral consequences.

W29. Cholinergic Activation Causes Increases in Brain Neurotrophins and Suppresses Beta Amyloid Accumulation Using Nicotinic Receptors in 5xFAD Mice

David Blake, Jacob Kumro, Ashutosh Tripathi, Anil Pillai, Sergei Kirov, Jeremy Sword, Alvin Terry*

The cholinergic forebrain or nucleus basalis of Meynert (nbM) provides acetylcholine to the entire cortical mantle and degenerates sooner than other brain regions during Alzheimer's disease (AD). The current frontline AD therapy of cholinesterase inhibitors improves cognition for about half of a year until becoming ineffective and often associates with peripheral cholinergic side effects. Our previous research demonstrated that intermittent, instead of continuous, electrical stimulation of the nbM improves working memory in an adult primate model. Here we implanted bilateral electrodes into the nbM of

4-month-old wild-type and 5xFAD mice. They received 1-hr of daily nbM intermittent stimulation at 100uA until the age of 9 months. Stimulation enhanced visuospatial memory when learning the Morris water maze task. However, only nbM-stimulated 5xFAD mice demonstrated significantly enhanced performance of the probe test. In both genetic backgrounds, treatment increased expression of the ligand mNGF as well as the neurotrophic tyrosine receptor kinases TrkA and TrkB receptors. Stimulation also reduced expression of the amyloidogenic enzyme beta-site APP cleaving enzyme 1 (BACE1), as well as reducted Aβ42 concentration. To determine the necessity of the different subtypes of cholinergic receptors, we administered non-selective and selective cholinergic antagonists in adjunct with stimulation to see which receptor subtypes were necessary in altering TrkA and BACE1 expression. A conditional knockout of alpha-7-nicotinic acetylcholine receptors further supported the pharmacology study that concluded the necessity of this specific receptor in the elicitation of the stimulation response. Cholinergic release activates neurotrophic pathways and suppresses beta amyloidogenesis through nicotinic alpha-7 receptors.

W30. Cardioprotection Following Myocardial Infarction by Hypothalamic Oxytocin Neuron Activation

David Mendelowitz, Kate Schunke, Matt Kay*

Disruption of cardiac parasympathetic activity is a common hallmark of a variety of cardiovascular diseases including myocardial infarction (MI). Myocardial ischemia and MI are accompanied by a marked autonomic imbalance with sympathetic overactivity and reduced parasympathetic cardiac vagal activity. Reduced vagal drive to the heart is a strong independent risk factor for life-threatening arrhythmias and sudden cardiac death while several experimental studies have shown that increased cardiac vagal activity exerts cardioprotective effects against ischemic injury. The paraventricular nucleus of the hypothalamus (PVN) is an important site of autonomic control, and there are direct projections from the PVN to parasympathetic cardiac vagal neurons (CVNs) that co-release oxytocin. Here, we provide critical new information for the field that identifies a novel target and downstream molecular changes that restore parasympathetic cardiac tone and reduce cardiac dysfunction and the incidence of arrhythmias following MI. In a rat model of MI, with ligation of the left anterior descending coronary artery (LAD), animals develop ischemia, arrhythmias and mortality similar to the clinical consequences of an acute MI. We show that LAD-ligated animals have reduced endogenous excitatory oxytocin-mediated neurotransmission to parasympathetic neurons in the brainstem. We further show that selective and chronic chemogenetic activation of hypothalamic PVN oxytocin neurons restores synaptic release of oxytocin, increases parasympathetic activity to the heart, substantially improves metabolic homeostasis, and reduces the incidence and initiation of arrhythmias, inflammation, fibrosis, and mortality.

W31. Regulator of G-Protein Signaling 14 (RGS14) Alters Behavioral and Pathological Responses Due to Kainic Acid-Induced Status Epilepticus

Nicholas Harbin, Daniel Lustberg, David Weinshenker, John Hepler*

Regulators of G-protein signaling (RGS) proteins are critical for proper regulation of receptor-mediated signaling in the central nervous system and elsewhere. One such RGS protein, RGS14, is highly expressed in pyramidal cells of area CA2 of the hippocampus and interacts with multiple signaling pathways to suppress calcium influx, neuronal excitability, and synaptic plasticity. Recent reports have demonstrated a protective function of RGS14 against injury in both the heart and liver. Therefore, we hypothesized that RGS14 may be protective within the hippocampus after excitotoxic injury (e.g. status epilepticus or SE). To test this hypothesis, we induced SE in wild-type (WT) and mutant RGS14 knockout (RGS14 KO) mice using kainic acid (KA). We evaluated behavioral responses during SE and probed for RGS14 expression and seizure-induced pathology in the days following SE in both genotypes. Using a modified Racine scale and mortality as measures of seizure severity, we found RGS14 KO mice reach higher stage seizures faster and die quicker during SE compared to WT mice. Western blotting and immunohistochemistry of hippocampal tissue from WT mice revealed a striking and significant upregulation of RGS14 after SE starting 1 day post-SE, notably in pyramidal cells of area CA1. Using microtubule associated protein 2 (MAP2) as a proxy for neuronal damage, we observed a significant loss of MAP2 expression in area CA1 in KA-treated RGS14 KO mice but not WT mice at later time points, suggesting a neuroprotective function of RGS14. Using ionized calcium binding adaptor molecule (IBA1) and glial fibrillary acidic protein (GFAP) expression as markers of microgliosis and astrogliosis, respectively, we found that both markers were upregulated following KA-induced seizures in WT mice, but were unchanged in RGS14 KO mice. Taken together, these results suggest that RGS14 plays an essential role in regulating behavioral and pathological response to seizure injury in the hippocampus.

W32. A3 Adenosine Agonists: Novel Therapeutics to Prevent Traumatic Brain Injury Induced Cognitive Impairment in Rodents

Monica Goodland, Michael Niehoff, Susan Farr, Daniela Salvemini*

For survivors of traumatic brain injury (TBI), a key factor to high quality-of-life is cognitive functioning. Changes that can occur include impaired thinking, memory, and learning. Cognitive impairment poses a large public health concern as it is estimated that up to 50% of mild TBI (mTBI) survivors will develop CI and there is no FDA approved treatment. Previously, we demonstrated that MRS5980, a highly selective A3 adenosine receptor agonist (A3AR), given 1h post injury prevented the development of CI 4 weeks after mice were subjected to a weight-drop model of mTBI, corresponding with reduced markers of neuroinflammation. Here, we investigated how far out post injury we can treat mice with MRS5980 and retain their protective effects. This approach is more clinically relevant for patients who do not seek care immediately post trauma. Mice were subjected

to either sham procedure or weight-drop TBI, as described previously. Injured mice were then divided into experimental groups receiving vehicle or MRS5980 (1 mg/kg I.P.) at 1h, 24h, or 72h post procedure. Sham mice received vehicle. MRS5980 or vehicle treatment continued every 48h for the duration of the study. Extensive behavioral testing was conducted 4 weeks post trauma to assess activity levels, anxiety, learning, memory, and depressive behaviors. We found no difference in activity, anxiety, or depressive behavior between groups. Learning and memory were assessed via novel object recognition (NOR) and T-maze paradigms. Learning and memory were preserved in 1h and 24h treatment groups compared to injured, vehicle treated mice. Interestingly, mice who began treatment 72h post trauma had preserved memory in the T-maze test, but not NOR. Highly selective A3AR agonists exemplified by MRS5698 are in advanced preclinical trials for pain and neuroinflammatory conditions. The present study supports MRS5980 as a potential therapeutic for TBI-induced cognitive impairment, addressing a chasm of unmet medical need.

W33. Effects of Psilocin on 5-HT2A L5P Neurons

Gavin Schmitz, Yi-Ting Chiu, Bryan Roth, Melissa Herman*

Psilocin, the active compound in psilocybin, was recently granted breakthrough drug status by the Food and Drug Administration due to its potential as a treatment for refractory depression. Despite promising clinical findings, the underlying signaling mechanisms and brain region-specific effects of psilocin and other psychedelic drugs remain unclear. The psychoactive effects of psychedelics are attributed to activation of serotonin (5-Hydroxytryptamine, or 5-HT) 2A receptors (5-HT2ARs). A significant hub for these effects is the Prefrontal Cortex (PFC). Focal application of psilocin (10mM) onto undifferentiated Layer 5 Pyramidal neurons in the prelimbic PFC of wild-type mice produced variable effects on firing (increase, decrease, or no change). 2A+ layer 5 pyramidal neurons in the mouse prelimbic PFC were identified in transgenic inducible td Tomato labeled mouse. Focal application of psilocin increased firing in all 5-HT2A+ neurons but did not result in any significant changes in inhibitory or excitatory synaptic transmission (sEPSC, mEPSC, or sIPSCs). Application of the 5-HT2C antagonist RS102221 (5mM) prior to psilocin administration failed to block the increased firing with application of psilocin. However, application of the 5-HT2A antagonist M100907 (100nM) prior to psilocin administration blocked the increase in firing with psilocin administration. Furthermore, application of the Gq inhibitor FR100907 prior to psilocin administration also blocked the increase in firing with psilocin administration. These results demonstrate that psilocin selectively increases the activity of 5-HT2A-containing Layer 5 PFC pyramidal neurons via a 5-HT2A receptor-dependent mechanism. Additionally, this effect is dependent upon signaling via the Gq G protein. Collectively, these data provide important insight into the neurobiological mechanisms underlying the effects of psilocin in the PFC that may be implicated in the therapeutic effects of psilocybin for the treatment of anxiety and depression in patients.

W34. Intraparenchymal Administration to the Striatum of a Barcoded AAV Library for the Characterization of Capsid Tropisms in Rodents and Non-Human Primates

Jared Smith, April Giles, Elad Firnberg, Bradley Hollidge, Samantha Yost, Jenny Egley, William Henry, Subha Karumuthil-Melethil, Joseph Bruder, Ye Liu, Olivier Danos, Andrew Mercer*

Adeno-associated viral (AAV) vectors are increasingly used for gene therapy in the central nervous system (CNS) and there is a need for identifying optimal capsids for specific targets. In this study, we evaluated the tropism of a library of 118 AAV capsids following intraparenchymal delivery. This library consisted of approximately equal concentrations of 56 NAV® Platform vectors, 49 engineered AAV variants, and 13 commonly used AAVs. Each AAV vector was produced individually using a unique cis plasmid expressing GFP under the control of the universal CAG promoter and a unique barcode sequence allowing for measurement of the relative abundance of each capsid's genomes and transcripts in different tissues using next-generation sequencing (NGS). The library was administered intraparenchymally to the striatum of non-human primates (cynomolgus macaques, MRI-guided injection with convection enhanced delivery) and mice (C57BL/6, stereotaxic injection). These studies allowed for the direct comparison of each capsid in the pool and translation of findings between species. Biodistribution analysis revealed vector genomes and transcripts were most prominently found at the injection site and brain regions anatomically connected to striatum (e.g. cortex, globus pallidus, amygdala, thalamus, substantia nigra) but were almost undetectable in brain regions that have no connections with the striatum (e.g. hippocampus, cerebellum, spinal cord). Within these connected brain regions, NGS revealed that some capsids were not present at all whereas other capsids were preferentially abundant. Interestingly, library members were found to have distinct transduction profiles for different brain regions, suggesting that unique capsids may prefer different synaptic structures. Taken together, these findings highlight the importance of direct, simultaneous comparison of the performance of AAV vectors and reveal promising variants for specific therapeutic targets within the CNS.

W35. Simultaneous, Real-Time, Pharmacokinetic and Pharmacodynamic (Behavioral) Measurements of Psychoactive Drugs in the Brains of Awake, Ambulatory Rats

Julian Gerson, Kevin Honeywell, Murat Kaan Erdal, Nicole Emmons, Jenny Gibson, Kaylyn Leung, Joao Espanha, Kevin Plaxco, Tod Kippin*

Psychoactive drugs exert their behavioral effects via concentration-dependent actions upon neural circuits. However, to date, the temporal resolution with which we can measure these compounds is orders of magnitude too slow to capture the concentrations associated with altered physiological processes. Thus motivated, our group has recently developed a new technology, electrochemical aptamer-based sensors (E-AB sensors) that can detect physiologically relevant concentrations of specific drugs in-situ, in awake, freely behaving animals. Furthermore, we have developed a Feedback-Controlled automated drug delivery system capable of maintaining drug levels constant at a desired concentration level as a

method to probe within session/acute tolerance. Procaine and cocaine are two psychoactive compounds that, although similar in their chemical structure, elicit opposing behavioral effects when administered. By adapting a previously presented aptamer we have improved the sensitivity of our E-AB sensor to both drugs by an order of magnitude, as well as enhanced drift characteristics observed in vivo. Here, we tested this new technology on rats that have been administered procaine intravenously and measured the in-brain concentrations of this drug while performing concurrent locomotion and physiological monitoring. We successfully measured procaine concentrations every ~10 s in real-time and generated subject-specific full pharmacokinetic profiles which are compared to the pharmacodynamic (behavioral) profile. Increases in procaine concentration coincide with decreased locomotion. We also show in vitro data suggesting a route forward for the detection of cocaine at physiologically relevant concentrations in rats. In conclusion, we have developed a novel, potentially revolutionary, technology that can measure the pharmacokinetics of psychoactive drugs within the brains of awake, freely behaving animals.

W36. Chemogenetic Activation of Intracardiac Cholinergic Ganglia Neurons Reduces the Incidence of Arrhythmias after an Acute Myocardial Infarction

Bridget Alber, Jhansi Dyavanapalli, Aman Gill, David Mendelowitz, Matthew Kay*

Intracardiac cholinergic ganglia (ICG) neurons receive excitatory input from vagal pre-ganglionic fibers and are critical for the transmission of parasympathetic drive throughout the heart. During disease, electronic vagal stimulation improves cardiac function and reduces arrhythmias. However, vagal stimulation is not selective for efferent or cholinergic fibers and implanting an electronic device before unanticipated episodes of cardiac infarction is not clinically feasible. We addressed these limitations by testing the hypothesis that ICG activation immediately after an infarction would reduce arrhythmia incidence and improve ventricular function. ICG cholinergic neurons were chemogenetically activated via selective expression of excitatory hM3Dq DREADDs after injecting floxed DREADDs into the pericardium of neonatal rats selectively expressing Cre recombinase in cholinergic neurons (ChAT-cre rats). At 8 weeks, hearts were excised for ex-vivo studies to measure heart rate (HR), left ventricular developed pressure (LVDP), and arrhythmia incidence. In healthy hearts, CNO decreased HR and LVDP for the duration of the experiment (2 hrs). To study ICG activation after infarction, hearts received CNO or saline after ligation of the left anterior descending coronary artery. The ECG was analyzed to assess arrhythmia incidence, including non-sustained and sustained ventricular tachycardia and fibrillation. Preliminary results indicate that ICG activation after infarction stabilizes HR and reduces arrhythmia incidence and infarct size. These outcomes are likely mediated in part by ICG-mediated coronary artery dilation and increased coronary flow. Altogether, our studies demonstrate that cholinergic ICG activation following a MI elevates cardiac parasympathetic drive to protect against arrhythmias and ischemic damage.

W37. A Miniature Kinematic Coupling Device for Mouse Head Fixation

Su Jin Kim, Alexander Slocum, Benjamin Scott*

Head immobilization is widely used in neuroscience studies to facilitate sensory stimulus control, behavioral monitoring, and neurophysiological recordings. Mechanical stability and repeatable positioning are particularly important for cellular resolution imaging or manipulation experiments. Headplates using kinematic coupling principles have been developed for micron-scale stability and repeatability in rats (Scott et al. 2013, Rich et al. 2018). Here we describe a device that extends this technology to mice. We designed a head-fixation system based on the Maxwell kinematic coupling system. The clamp was an aluminum mount with three vee grooves, oriented at 120 degrees relative to each other. The headplate was a stainless steel triangle with three half spheres at the vertices. Neodymium magnets attached to the clamp were used to provide the clamp force. We assessed registration accuracy using two-photon microscopy (2PM) of fluorescent beads fixed to the headplate. Initially registration accuracy (RMS displacement) was 2.9µm in the lateral axis, 3.7µm in the vertical axis, and 1.4µm in the z-axis. Electron microscopy of the contact surfaces revealed mesoscale ridges and grooves on the clamp and the headplate spheres. We replaced the half spheres with ruby spheres, and improved accuracy to 0.45µm in x, 0.65µm in y, and 0.4µm in z. We assessed stability via 2PM of hippocampal neurons in awake, behaving mice. RMS displacement was <4µm within the imaging plane, small enough for correction by standard image registration algorithms. These results suggest the mechanical stability of the system is sufficient for cellular resolution imaging in awake, behaving mice. We anticipate that the system reported here may facilitate experiments in mice where high precision and stability are required, such as imaging experiments using voluntary head restraint, time-lapse developmental studies, or registration of the same subject across multiple instruments.

W38. Sleep Deprivation Induces Opposing Effects on Dendritic Spine Remodeling in Amygdala-Hippocampal Memory Circuit

*Lindsay Rexrode, Matthew Tennin, Caleb Young, Ratna Bollavarapu, Jake Valeri, Harry Pantazopoulos, Barbara Gisabella**

Sleep is critical for memory consolidation, and disturbances in sleep and memory processing are common in psychiatric disorders. Despite recent advances, the morphological and molecular processes underlying memory consolidation in brain circuits regulating emotional memories are currently unknown. Chronic stress is a key feature associated with psychiatric disorders. Previous studies in rodents showed that chronic stress differentially affects dendritic spine density, resulting in increased dendritic spines in amygdala and dendritic atrophy in the hippocampus. These findings suggest that these two key regions may also be differentially regulated during sleep. We tested the hypothesis that sleep deprivation differentially affects dendritic spines in the mouse amygdala and the hippocampus.

We used viral vector labeling of dendric spines combined with confocal imaging and three-dimensional (3D) analysis in sleep deprived and control male C57/Bl6 mice to determine how sleep deprivation affects dendritic spine density and size on specific

dendritic segments of CA1 hippocampal pyramidal cells and amygdala neurons. Immunohistochemistry and quantitative microscopy for phosphorylated cofilin, a marker involved in dendritic spine downscaling, was used as a first step in examining molecular markers involved in synaptic changes.

We observed region- and branch-specific synaptic downscaling in the hippocampus, supporting the theory of synaptic downscaling during sleep. In the amygdala, we observed opposing effects. Sleep deprivation resulted in decreased dendritic spine density during sleep, particularly in mushroom spines, and increased neck length and decreased spine head diameter in mushroom dendritic. Furthermore, we observed decreased density of phosphorylated cofilin immunoreactive cells in the amygdala of sleep deprived mice.

Our results demonstrate differential effects of sleep deprivation on dendritic spines between the hippocampus and amygdala. These results reflect the reported effects of chronic stress in these two regions. Our data provide key insight into the morphological correlates of memory consolidation during sleep as well as the processes that may be affected in this circuit in psychiatric disorders.

W39. Divergent Opioidergic Brainstem Pathways That Mediate Pain-Breathing Interaction

*Sung Han**

Breathing and pain perception seem to be unrelated critical brain functions, yet they influence each other. Severe pain induces hyperventilation, whereas paced slow breathing alleviates pain perception. However, a neural circuit-based understanding of pain-breathing interaction is lacking. Here we report that Oprm1 (μ-opioid receptor)-expressing neurons in the lateral parabrachial nucleus (PBL) are crucial for regulating breathing, pain, and their interaction. The PBL-Oprm1 activity is tightly correlated with the breathing rhythm, and noxious stimuli simultaneously elevate both. Manipulating PBL-Oprm1 activity collectively modulates breathing rhythm and negative affects, such as pain and anxiety. Furthermore, we find that the association of pain and breathing is mediated by two non-overlapping but reciprocally connected Oprm1 subpopulations in the core and shell of the PBL, which diverge to the central amygdala and medullary respiratory center, respectively. These results uncover the role of the parabrachial opioidergic pathways in regulating basal respiratory rhythm and pain-breathing interaction.

TH1. Remifentanil Self-Administration in Mice Promotes Sex-Specific Cortico-Striatal Dysfunction Underlying Deficits in Cognitive Flexibility and Reduced Control Over Drug Taking

Matthew Hearing, Eden Anderson, Abbi Quimet*

A prevailing model in the addiction field is that the transition from voluntary to uncontrolled drug use arises from drug-induced hypofunction of frontal cortex circuits responsible for flexible decision-making and top-down inhibitory control and a shift in control of drug use from prefrontal cortex circuits to habit-based circuits. A major gap in this account is a lack of empirical evidence to support it, in particular with opioids. We find that 2-wk of self-administering (SA) remifentanil causes a long-lasting hypoactive basal state in prelimbic cortex (PrL) pyramidal neurons in females evidenced by a decrease in ex vivo excitability that is paralleled by an increase in firing capacity. Alternatively, after 4-wk of SA, females exhibited an overall reduction in excitability and firing. Unpublished data indicate that a similar shift in activity states occurs in males following 4- and 6-wk of SA. These adaptations align with sex-specific changes in excitatory:inhibitory synaptic transmission, with preliminary findings suggesting adaptations are more pronounced in pyramidal neurons projecting to the nucleus accumbens core (Core). Published and unpublished data indicate that time-dependent shifts in PrL excitability/firing align temporally with the emergence of impaired cognitive flexibility followed by increased habit-like drug-seeking that is more pronounced in females and can be restored with chemogenetic increases in neural activity. Further, preliminary studies indicate that inhibition of the PrL effectively reduced drug intake after 2- and 4-wk of SA in males but only 2-wk in females. Additional studies will examine parallel changes in PrL-Core and dorsal striatal (habit) sub-circuits circuits. These data provide novel insight into progressive neural adaptations driving maladaptive behavior and highlight a need to tailor treatment to the individual (e.g. biological sex) and neuroadaptations that progressively emerge during the development of addiction.

TH2. Junk-Food Diet Induced Changes in Nucleus Accumbens Glutamatergic Plasticity and Food-Cue Motivated Behavior

Tracy Fetterly, Carrie Ferrario*

Changes in brain reward centers, such as the Nucleus Accumbens (NAc), contribute to over-eating and craving that drives the development and persistence of obesity in humans. In rats, cue-triggered food-seeking is enhanced in obesity-prone males as compared to obesity-resistant males. Furthermore, this behavior is attenuated by blocking NAc calcium-permeable AMPA receptors (CP-AMPARs). After eating a sugary, fatty junk-food diet, NAc CP-AMPAR expression and transmission is increased, suggesting that junk-food may enhance motivational responses to food cues. In addition, synaptic increases in CP-AMPARs require a brief junk-food deprivation period in which rats are returned to standard chow. But the mechanism driving CP-AMPAR recruitment is unknown. Here we determined the input-specificity of CP-AMPAR increases and the mechanism allowing for

synaptic insertion of CP-AMPARs. Furthermore, given the role of NAc CP-AMPARs in cue-triggered motivation, we examined junk-food induced changes in motivational responses to a food-cue using conditioned reinforcement. We used whole-cell patch clamping in combination with a viral optogenetic strategy to record CP-AMPAR transmission from either the medial prefrontal cortex (mPFC) or basolateral amygdala (BLA) inputs to the NAc. After junk-food consumption and deprivation, we see enhanced CP-AMPAR transmission in mPFC-to-NAc inputs in obesity-prone rats, but no differences between groups in BLA-to-NAc inputs. In addition, our data suggest that artificially decreasing activity in the NAc is sufficient to recruit CP-AMPARs in male obesity-prone rats. This suggests that increases in CP-AMPARs may be a compensatory response to reduced excitatory input during junk-food deprivation. Finally, preliminary data suggest that eating junk-food increases the reinforcing properties of a food-cue in obesity-prone rats. Ongoing studies are examining potential links between junk-food induced enhancements in behavior, NAc CP-AMPARs, and mPFC activity.

TH3. Rat Infralimbic Projections to the Nucleus Accumbens Shell Encode Cocaine Extinction Contingencies During Temporally Specific Windows

Kelle Nett, Matthew McGregor, Alexa Zimbelman, Ryan LaLumiere*

Prior evidence indicates that the ventral portion of the medial prefrontal cortex, known as the infralimbic cortex (IL), mediates the ongoing inhibition of cocaine seeking, specifically through its projections to the nucleus accumbens (NA) shell. Our own data indicates IL activity during the 20 s immediately following an unreinforced lever press is critical for extinction encoding. However, whether IL-NAshell encodes extinction learning remains unclear. Moreover, it is unknown whether the critical period for this encoding is limited to the initial 20 s period after a lever press or extends longer. To address this issue, we used an activity-controlled, “closed-loop” optogenetic approach in which IL-NAshell activity was silenced following an unreinforced lever press for the first or second 20 s after the lever press (0-20 s and 20-40 s, respectively) during extinction training. Male and female Sprague-Dawley rats received bilateral injections of AAV-CaMKII-eArchT3.0 into the IL and bilateral fiber optic probes above the NAshell. Rats then underwent two weeks of daily 2 h cocaine self-administration sessions, in which active lever presses produced a cocaine infusion (0.33 mg/kg/inf), light/tone cues, and retraction of the active lever for 20 s or 40 s. Following this, rats underwent 5 d of manipulated extinction sessions (30 min), in which active lever presses only led to lever retraction and bilateral illumination of IL terminals in the NAshell (from 0-20 s or 20-40 s). Following 5 d with inhibition, each rat underwent 7 d of full length (2 h), unmanipulated extinction sessions in which lever presses only resulted in a lever retraction. The results indicate that IL-NAshell inhibition from 0-20 s post lever press, and not 20-40 s post lever press, significantly impairs extinction learning during the manipulated sessions and the retention of this extinction learning, as assessed during the unmanipulated sessions. These findings point to a critical window following an unreinforced lever press during which activity from IL-NAshell encodes the new extinction contingencies between the lever press and lack of a cocaine reinforcer. Moreover, combined with previous work, the results suggest that plasticity underlying extinction encoding occurs, at least in part, beyond the IL itself and in the synaptic inputs to the NAshell.

TH4. High Dose THC During Adolescence Increases Behavioral Lability to Stress and Thc Later in Life Linked to Perturbations in Astrocytes

Jacqueline-Marie Ferland, Randall J. Ellis, Gregory Rompala, Joseph A. Landry, James E. Callens, Graeme Betts, Mason M. Silveira, Catharine Winstanley, Yasmin L. Hurd*

Despite the belief that cannabis is relatively harmless, exposure during adolescence is linked to the genesis of several psychopathologies including cannabis use disorder (CUD), emotional dysregulation, and cognitive deficits. A growing concern regarding adolescent use is the fact that the potency of delta-9-tetrahydrocannabinol (THC) has increased more than fourfold compared to the 1990s. There remains a dearth of evidence on the protracted effects of high dose THC on behaviors relevant to many psychiatric conditions and molecular mechanisms underlying these effects. To provide causal insights into the long-term effects of adolescent THC exposure, we leveraged a translational approach that integrates cutting-edge molecular techniques with complex behavioral assays to dissect the impact of adolescent THC dose on reward, stress reactivity, and decision making. High dose THC led to greater sensitivity to stress and cognitive deficits after re-exposure to THC in adulthood, phenotypes associated with psychiatric disorders including addiction. Computational modeling of rat and human decision-making data showed remarkably comparable learning rates between species. Strikingly, the high dose rats showed behavioral strategies akin to individuals with CUD, providing a strong translational link between the impact of high dose THC on decision making and addiction vulnerability. Single-cell deconvolution of RNA sequencing of the basolateral amygdala (BLA), a region linked to stress and cognition, revealed that the increased stress reactivity seen in high dose animals was linked to perturbations in astrocyte-specific genes and morphology. Moreover, BLA Gfap expression directly correlated with the cognitive deficits measured in the decision-making task. Critically, these perturbations were distinct from those seen in low dose animals, suggesting the synergistic impact of THC dose and environmental experience on behavior relevant to the development of psychopathologies.

TH5. A Role for Ventral Pallidum Glutamate Neurons in the Effects of Stress on Heroin Sensitization

Carley Miller, Nicholas Fayette, Brandi Wiedmeyer, Jasper Heinsbroek*

Stress is an important risk factor for the development of opioid use disorder (OUD) and stressful events often trigger drug relapse. Similarly, animal models show that acute stress modulates the acquisition and reinstatement of drug self-administration and alters the sensitized locomotor responses to drugs of abuse. Despite these behavioral correlates, our understanding of brain regions mediating the effects of stress on OUD is incomplete. One brain region of interest is the ventral pallidum (VP), a major downstream target of the mesolimbic reward system and a recipient of glutamatergic innervation from stress reactive brain regions. In particular, glutamatergic neurons of the VP have been linked to stress and aversive behaviors. Thus, our study sought to examine the role of VP glutamate neurons during exposure to acute stress and the subsequent development of locomotor sensitization to heroin using Vglut2-IRES-Cre mice. Mice were exposed to acute (1 h)

immobilization stress 24 h or 10 d prior to undergoing heroin sensitization. During these procedures, VP glutamate neuronal activity was monitored in vivo with a miniscope system for imaging calcium activity in the VP using implanted GRIN lenses. These ongoing studies aim to better characterize the involvement of the VP glutamate neurons in acute stress and behavioral sensitization to heroin.

TH6. Reelin Protein Marks Cocaine-Sensitive Drd1+ Medium Spiny Neurons and Modulates the Transcriptional and Physiological Response to Dopamine

Kasey Brida, Robert A. Phillips, M. Natalie Davis, Kelsey Montgomery, Kristen R. Maynard, Keri Martinowich, Jeremy J. Day*

Reelin, a large, secreted glycoprotein encoded by the gene Reln, is expressed at high levels in the adult striatum, hippocampus, and cerebellum. Reln expression plays a critical role in brain development and experience-dependent plasticity. While the role of reelin protein in neurodevelopment has been extensively studied, reelin's cellular and molecular role in the adult brain remains to be characterized, despite genetic links to neuropsychiatric disorders, such as psychostimulant abuse. To assess Reln mRNA distribution within specific cell types of the rat nucleus accumbens (NAc), we queried a recently described transcriptional atlas generated from single-nucleus RNA-seq of rat NAc tissue collected following acute cocaine exposure. This dataset demonstrated that Reln mRNA marks a population of cocaine-responsive Drd-1+ medium spiny neurons (MSNs). These results were mirrored in postmortem human brain tissue, where multiplexed fluorescent in-situ hybridization showed enrichment of RELN mRNA in NAc Drd1+ MSNs. We next designed a CRISPR sgRNA targeting the Reln promoter, allowing us to bidirectionally manipulate Reln mRNA and protein levels with CRISPR activation or CRISPR interference. Notably, CRISPR activation of Reln in rat primary striatal neuron cultures enhanced stimulus-dependent transcription of immediate early genes following dopamine stimulation. Likewise, knockdown of Reln blunted the dopamine-induced increases in MSN firing rate, without altering baseline electrophysiological properties. These results suggest that Reelin may contribute to dopamine-dependent transcriptional and physiological changes caused by cocaine. Ongoing studies are assessing the effects of CRISPR-mediated Reln manipulations on cocaine-induced behavioral responses.

TH7. Neuronal PAS Domain Protein 4 (Npas4) regulates cocaine-conditioned behaviors and synaptic transmission in a cell type-specific manner

Brandon Hughes, Stefano Berto, Ben Siemsen, Rose Marie Akiki, Evgeny Tsvetkov, Daniel Wood, Kirsten Snyder, Penrod Rachel, Michael Scofield, Taniguchi Makoto, Christopher Cowan*

Relapse can be triggered in individuals with substance use disorder by cues in the environment associated with prior drug use, though the neurobiological mechanisms that produce these powerful and enduring relapse-promoting memories are poorly understood. Here we show that the activity-dependent transcription factor, Neuronal PAS Domain Protein 4 (Npas4), plays an essential role in promoting cocaine-associated behavior. Npas4

in the nucleus accumbens (NAc), a key brain reward region, is induced by cocaine experiences in a small subset of neurons, including dopamine D1 and D2 receptor-expressing medium spiny neurons (MSNs). Using a novel Npas4-TRAP (Targeted Recombination in Activated Populations) mouse, we show that NAc neurons inducing Npas4 during cocaine experience are required for subsequent drug-seeking behavior. Moreover, Cre-dependent reduction of Npas4 in D2-MSNs, but not D1-MSNs, reduced both non-contingent cocaine conditioned place preference (CPP) and cue-induced drug seeking following cocaine self-administration. We also find that Npas4 expression in NAc D2-MSNs opposes a cocaine-dependent increase in dendritic spines and strengthening of medial prefrontal cortex inputs, a major NAc afferent required for both drug-context memories and discreet cue-induced cocaine seeking. Finally, transcriptomic analysis from the NAc revealed that cocaine experience-induced Npas4 influences the expression of numerous downstream gene targets that may regulate drug-context learning. Together our findings reveal that Npas4 promotes homeostatic cellular plasticity that limits D2-MSN activation to facilitate maladaptive cocaine seeking behavior.

TH8. Prenatal THC Exposure Promotes Transcriptional Network Changes in the Ventral Tegmental Area and Promotes Reward Seeking and Phasic Dopamine Terminal Release in the Adult Rat Offspring

Miguel Lujan, Cali Calarco, Basu Mahasweta, Sonia Aroni, Seth Ament, Gautam Kumar, Miriam Mellis, Mary K Lobo, Joseph Cheer*

Marijuana is the most common illicit drug used by pregnant women and is associated with offspring's attention and learning deficits from early childhood until later in life. However, the impact of prenatal cannabis exposure (PCE) on maladaptive gene expression changes and its consequences on accumbal dopaminergic encoding of reward-seeking behavior have not been specifically addressed in the adult progeny. In order to address this, we conducted transcriptomic analyses (RNA-seq) in brain samples of PCE adult rats. Weighted Gene Co-expression Network (WGCNA), Differential Gene Expression (DGE) and Gene Ontology (GO) analyses all identified single-gene and network-wide alterations on lipid metabolism as well as mitochondrial, and synaptic plasticity processes related to PCE. Furthermore, the addition of sex as a co-variate revealed homeostatic adaptations in female but not in male rats, which failed to cope with the in utero THC insult. A separate cohort of PCE rats underwent operant training to obtain sucrose pellets rewards under different reinforcement schedules. Adult PCE rats showed maladaptive reward-seeking behaviors, loss of inhibitory control and exhibited exacerbated mesoaccumbal dopamine release (GrabDA) in response to reward-associated cues. Congruent with our transcriptome findings and with our previously published work, these dopaminergic alterations where more prominent in the male progeny. Our results suggest that a series of complex, long-lasting transcriptomic maladaptations to prenatal THC exposure are accompanied by alterations in motivational function, inhibitory control and dopaminergic encoding of natural rewards and their associated environmental cues.

TH9. Novelty-Induced Locomotor Behavior Predicts Heroin Vulnerability in Males while Network-Based Clustering Predicts Vulnerability in Both Sexes

Brittany Kuhn, Nazzareno Cannella, Carter Allen, Ayteria Crow, Analyse T. Roberts, Veronica Lunerti, Massimo Ubaldi, Gary Hardiman, Leah Solberg Woods, Dongjun Chung, Roberto Ciccocioppo, Peter W. Kalivas*

There has been a significant rise in opioid use disorder (OUD) in the United States over the past decade, making it imperative to gain a better understanding of the behavioral characteristics underlying OUD vulnerability. In the current study, models of individual variation in addiction-related behaviors were employed to better model phenotypic heterogeneity within the human condition of OUD. Male and female heterogeneous stock rats first underwent an open field test. Next, rats underwent 3 weeks of long-access (12-hr) heroin self-administration training, followed by a progressive ratio test to determine the motivation to work for the drug and a heroin-induced reinstatement test. Six days of extinction training followed prior to a test for cue-induced reinstatement. After testing, rats were characterized based on a high level (high-responder, HR) or a low level (low-responder, LR) of novelty-induced locomotor behavior during the open field test. The HR/LR model is commonly used to examine individual variation in the acquisition of drug taking. In males, HR rats consumed more heroin, worked harder for an infusion of heroin, and showed greater cued reinstatement relative to LRs. Conversely, in females, there were no phenotypic differences. These data suggest that novelty-induced locomotor behavior is a trait only predictive of OUD vulnerability in males, not females. To better model how behaviors interact with one another to confer OUD vulnerability in both sexes, a Bayesian stochastic block model was applied to the data. Three distinct subpopulations emerged that predicted OUD vulnerability in both sexes, although females showed a more vulnerable phenotype, akin to what is observed in humans. These data highlight the advantage of modeling how multiple behaviors, and not a singular trait, interact with one another to predict OUD vulnerability in both males and females. The neurobiological mechanisms mediating group differences are currently under investigation.

TH10. Pain Catastrophizing is Associated with Increased Alcohol Cue-Elicited Neural Activity Among Individuals With Alcohol Use Disorder

Steven Nieto, Erica Grodin, Elizabeth Burnette, Catherine Cahill, Lara Ray*

Comorbid pain and alcohol use disorder (AUD) are highly prevalent and costly conditions. Emotional components of pain, such as pain catastrophizing, can exacerbate painful experiences, thereby contributing to problematic alcohol use as a coping mechanism. Pain catastrophizing, but not pain intensity, is associated with tonic levels of alcohol craving in heavy drinkers. The current study examined the association between pain catastrophizing and alcohol cue-elicited brain activation in individuals with AUD. Non-treatment seeking heavy drinkers with AUD (n=45; 28 males) completed self-report measures of pain catastrophizing and alcohol use/problems as part of a clinical trial of the neuroimmune modulator ibudilast (NCT03489850). Participants completed an fMRI scan to assess neural

activation to alcohol cues one week into the medication trial. Multiple linear regression examined whether pain catastrophizing predicted cue-induced activation in a priori regions of interest, namely the dorsal and ventral striatum. An exploratory whole-brain analysis was conducted to assess the relationship between pain catastrophizing and neural alcohol cue reactivity. Pain catastrophizing predicted greater cue-induced activation in the dorsal ($B=0.006$; $p<0.05$) but not ventral striatum controlling for medication. Pain catastrophizing was positively associated with neural activation to alcohol cues in regions including the bilateral thalamus, left precuneus, and left frontal pole. Greater pain catastrophizing is associated with greater cue-induced neural activation in brain regions sub-serving habits and compulsive alcohol use. These findings provide initial support for a neural mechanism by which pain catastrophizing may drive alcohol craving among individuals with AUD.

TH11. The Fragile X Mental Retardation Protein Regulates Drug-Related Behaviors via Its Function in D1 Receptor-Expressing Cells of the NAc

Jessica Huebschman, Elsbeth Chow, Elizabeth Harrison, Yuhong Guo, Laura Smith*

Substance use disorders are characterized by a shift in voluntary drug-taking to compulsive drug-seeking and -taking behaviors, which persist despite negative consequences and remain prone to relapse after periods of abstinence. Previous work suggests that the fragile x mental retardation protein (FMRP), an RNA-binding protein that regulates synaptic plasticity, is required for cocaine-induced synapse elimination in the striatum, a brain region critical to reward function. Moreover, loss of FMRP, either broadly or in the ventral striatum (nucleus accumbens; NAc), is capable of dampening cocaine-induced behaviors. In an intravenous cocaine self-administration (IVSA) task, mice lacking FMRP fail to make normal upward shifts in responding during dose-response testing and earn fewer cocaine infusions than wildtype (WT) mice under increasing schedules of reinforcement. Here, however, we find that loss of FMRP specifically in D1 dopamine receptor (D1R)-expressing cells of the NAc increases both cocaine conditioned place preference (CPP) and propensity to self-administer a low dose of cocaine, suggesting either that it functions in this cell type to suppress drug-taking, or alternatively, its absence in D1R, but not D2R, -expressing cells alters the normal balance of signaling in the NAc. Ongoing work in our lab is utilizing a cortical-striatal co-culture model to examine the role of FMRP in regulating synaptic plasticity and dendritic spine morphology in D1R-expressing cells following repeated exposure to a D1R agonist, which will provide further insight into FMRP's function in this cell type as it relates to drug-related behavior.

TH12. Long-Term Access to Fentanyl Vapor Leads to Compulsive-Like Behaviors in Male and Female Mice

Renata Marchette, Erik Carlson, Emma Frye, Leandro Vendruscolo, George Koob*

Rodent models are useful for understanding the mechanisms that underlie opioid addiction, but most preclinical studies have focused on the rewarding and consummatory aspects of opioids without components of compulsive-like drug taking or seeking. We aimed to

characterize several opioid-related behavioral measures in mice of both sexes using a model of vaporized fentanyl self-administration. Male and female C57BL/6J mice were trained to lever press for fentanyl vapor (5 mg/mL, 1.5 sec delivery, 1-min timeout) and then assigned to short access (1 h; ShA) or long access (6 h; LgA) conditions (10 sessions). Next, the mice were tested in a battery of behavioral tests, which were used to compare ShA and LgA groups and to create a correlation matrix. We did not see major sex differences across the behavioral tests, so data from males and females were pooled for the correlation analysis. Compared to ShA, LgA to fentanyl vapor led to escalation of intake, higher breakpoint in a progressive ratio (PR) test, in which the workload (i.e., the number of lever presses) for the next drug reinforcement increases progressively and decreased responding for fentanyl adulterated by the respiratory irritant capsaicin (i.e., to model punished drug taking). Moreover, mice allowed LgA to fentanyl exhibited greater hyperalgesia during spontaneous withdrawal and greater naloxone (1 mg/kg, intraperitoneal)-precipitated somatic signs of withdrawal. Both the ShA and LgA conditions showed a significant correlation between motivation in the PR test and escalation of fentanyl intake. For the LgA condition only, we found significant correlations between punished taking and 1) escalation of intake, 2) motivation in the PR test and 3) hyperalgesia during spontaneous withdrawal. The self-administration behaviors were not correlated with naloxone-precipitated signs of opioid withdrawal. These results support the hypothesis that compulsive-like opioid taking may be driven by motivational withdrawal but not somatic withdrawal.

TH13. Probing the Function of Neuronal Ensembles in Dorsomedial Prefrontal Cortex During Conditioned Reward Seeking

Roger Grant, Elizabeth Doncheck, Kelsey Vollmer, Kion Winston, Elizaveta Romanova, Jacqueline Paniccia, Bowen Christopher, James Otis*

Exclusive cell populations within the dorsomedial prefrontal cortex (dmPFC) have been shown to exert control over distinct aspects of reward seeking via their divergent activity patterns. However, response heterogeneity exists within these populations that is not fully explained by their projection target or gene expression profile. To address this unexplained response heterogeneity, we monitored the activity dynamics of putative dmPFC excitatory output neurons using in vivo two-photon calcium imaging (via AAVdj-CaMK2α-GCaMP6s) through a surgically implanted GRIN lens, while mice performed a Pavlovian sucrose conditioning task. Mice reliably acquired conditioned licking responses to a sucrose-associated cue, but not to an unpaired neutral cue. In line with previous studies, we observed a variety of dmPFC neuronal responses during this task. To better characterize these heterogeneous activity patterns, we performed unsupervised spectral clustering of dmPFC neuronal responses, and revealed five neuronal ensembles that each encode specific information related to delivery of a sucrose reward, presentation of reward-predictive cues, and behavioral responses to those cues. Single-cell tracking of neuronal responses across learning revealed unique ensemble activity patterns that emerged across daily training sessions and stabilized after learning, such that each ensemble's activity could be used to reliably predict unique aspects of the behavior task. Overall, our results characterize the complex dmPFC neuronal ensemble dynamics that predict reward

availability and initiation of conditioned reward seeking following cue-reward learning. However, the causal function of each ensemble for reward-seeking behavior remains less clear. In ongoing experiments, we are employing single-cell optogenetics to functionally manipulate the activity of each dmPFC neuronal ensemble in vivo, to determine their influence on both natural and drug reward-seeking behavior.

TH14. Sex Differences in Cognitive Deficits and Inhibitory Activity by Repeated Methamphetamine Exposure

Monserrat Armenta-Reséndiz, Antonieta Lavin*

Chronic METH users develop hypofrontality and concurrent deficits in working memory (WM). Hypofrontality resulting from METH abuse has been extensively reported, however, there is a dearth of studies regarding the influence of gender in the hypoactivity in PFC and cognitive deficits following repeated METH exposure. We explored the role of the estrogens in the cognitive deficits, PFC hypoactivity, and sensitization produced by repeated METH. We used 6 groups of rats (n=5-10 rats/group): Intact Female saline (IF SAL); ovariectomized saline (OVX SAL), male saline (M SAL), and their METH counterparts (IF METH, OVX METH, and M METH). All rats went through a METH sensitization regime or SAL. After 14 days of METH treatment (day 1 and 14, 1 mg/kg; days 2-13, 5 mg /kg) with locomotor evaluations on days 1 and 14, animals went through 7 or 28 days of home cage abstinence. On day 28 of abstinence, animals were challenged with a METH injection (1 mg/kg), and locomotor activity and temporal order memory (TOM) were assessed. We used different electrophysiological protocols in whole-cell clamp mode to assess intrinsic excitability and inhibitory activity [spontaneous inhibitory postsynaptic currents (sIPSCs), evoked inhibitory postsynaptic currents (eIPSCs), paired pule (PP)] in pyramidal neurons from layer V in mPFC at 7 and 28 days of abstinence. We found that M, IF, and OVX present a decrease in behavioral sensitization after 28 days of abstinence. We found that after 7 days of abstinence all the METH rat groups showed significant impairments in the TOM test, however, after 28 days of abstinence, only the IF group exhibited a significant recovery. After 7 days of abstinence the IF and M groups presented an increase in the frequency of sIPSCs, this effect suggests changes in the presynaptic activity. However, the amplitude of the spontaneous events was increased by METH exposure only in the M group, suggesting that M METH rats may exhibit changes also at the post-synaptic level. Together these results suggest a difference between M and IF regarding the recovery from TOM deficits after long abstinence suggesting that IF can recover faster from cognitive deficits. The OVX group shows deficits in TOM after long abstinence and a basal increase in inhibitory activity suggesting estrogens may play a role in the regulation of GABAergic transmission.

TH15. Within Subject Cross-Tissue Analyses of Epigenetic Clocks in Substance Use Disorder Postmortem Brain and Blood

Brenda Cabrera Mendoza, Laura Stertz, Katherine Najera, Sudhakar Selvaraj, Antonio L. Texeira, Thomas Meyer, Gabriel Fries, Consuelo Walss-Bass*

It has been suggested that there is possible accelerated biological aging in patients with substance use disorders (SUD). So far, the evaluation of epigenetic clocks, which are

accurate estimators of biological aging based on DNA methylation changes, has been limited to blood tissue in patients with SUD. Thus, the impact of epigenetic aging in the brain of individuals with SUD remains unknown.
Both postmortem brain (prefrontal cortex) and peripheral blood tissue from individuals with SUD (n=39), including alcohol (n=10), opioid (n=13), and stimulant use disorder (n=19), and non-psychiatric controls (n=10) were obtained from The University of Texas Health Science Center at Houston Brain Collection with Institutional Review Board approval. The DNA methylation profile of each sample was evaluated with Infinium Human Methylation EPIC BeadChip. DNA methylation values were used to calculate DNA methylation clocks -DNAmAge, DNAmAgeHannum, DNAmPhenoAge, DNAmGrimAge, and DNAmTL- and their respective measures of age acceleration with the Horvath's DNA Methylation Age Calculator (http://dnamage.genetics.ucla.edu). First, we assessed differences in the epigenetic clocks between individuals with and without SUD in brain and blood tissues, separately using a linear regression model. Then, we evaluated possible cross-tissue differences on the evaluated epigenetic clocks in brain and blood samples from the same individuals using a linear regression model.

We found a higher DNAmPhenoAge (beta=0.203, p-value=0.006) and lower DNAmTL (beta=-0.180, p-value=0.03) in blood from individuals with SUD compared to controls. SUD subgroup analysis showed a lower brain DNAmTL in subjects with alcohol use disorder, compared to stimulant use disorder and controls (beta=0.02, p-value=0.02). Cross-tissue analyses indicated a lower blood DNAmTL and a higher blood DNAmGrimAge compared to their respective brain values in the SUD group.

To the best of our knowledge, this is the first cross-tissue study investigating the relationship between brain and blood epigenetic age measures in postmortem tissues from individuals with SUD. This study highlights the relevance of tissue specificity in epigenetic aging studies, and suggests that peripheral measures of epigenetic clocks in SUD may depend on the specific type of drug used.

TH16. Circuit-Specific Endocannabinoid Regulation of Somatostatin Interneurons in the Nucleus Accumbens

Veronika Kondev, Sachin Patel*

The nucleus accumbens (NAc) is situated at the limbic-motor interface to guide adaptive decision-making and mediate appetitive and aversive behaviors. While a majority of the neurons in the NAc are long projections medium spiny neurons (MSNs), there is a small population of somatostatin (SOM+) interneurons that regulate MSN excitability and therefore influence NAc output. While these SOM+ neurons have been implicated in cocaine contextual conditioning, little is known about the role of these cells in aversive processing and stress responding. Here, we use in vivo fiber photometry to demonstrate that these SOM+ cells respond to footshock. Using slice electrophysiology, we further show that footshock enhances the excitability of these SOM+ cells. Given that the endocannabinoid system mediates neurotransmission in the NAc, we reveal that endocannabinoid signaling differentially regulates glutamatergic inputs onto these SOM+ cells from the basolateral amygdala (BLA), prefrontal cortex (PFC), and ventral hippocampus (vHIPP). These inputs also result in feedforward inhibition onto SOM+

interneurons that is further regulated by the endocannabinoid system. Finally, we show that the enhanced excitability caused by footshock exposure can be reversed by inhibiting endocannabinoid signaling. Taken together, these data present pathway-specific mechanisms mediating SOM+ control of local circuit networks within the NAc and provide evidence for the recruitment of these cells in stress responding.

TH17. Social Hierarchies Negotiate the Response to Psychosocial Stress in an Adult Female Mouse Model of Depression

Lydia Smith-Osborne, Anh Duong, Jonathan Fadok*

Depression is one of the most common psychiatric conditions of modernity, and it disproportionately affects women. Recently, there has been a generational trend of increased prevalence in adults. It has been postulated that this is due to the demands of competitive work environments, socioeconomic stress and social isolation. Why some thrive in such environments and others develop depression is poorly understood. Rodent models of social hierarchies can be studied to investigate the psychosocial stressors and neurobiology contributing to the depressive milieu. Female rodents in particular have been shown to establish hierarchies based upon unidentified intrinsic factors influencing sociability and stress.

We hypothesize that the protective effects of social partnerships contribute to stress susceptibility in a rank-based manner, reflecting the neurobiological signatures characteristic of rank. We perform our investigation in two aims – first to determine the role of rank in reward salience and identify neuroanatomical regions of involved in rank-skewed social interactions, and second to investigate differences in vulnerability to depression induced by social instability stress (SIS).

We find that mature adult females housed in dyads rapidly form stable hierarchies, but that rank was independent of innate anxiety or locomotor characteristics. Rather, we identify behavioral manifestations of intrinsic rank wherein subordinate animals are characterized as relatively high-stress in social interactions with a predilection for exploration and novelty-seeking behaviors, whereas dominant animals seek out social interactions and may be more susceptible to the psychosocial effects of long-term social isolation. These findings support the hypothesis that rank in females is determined by intrinsic traits rather than through 'winning' as in males, and identifies a stress-susceptible phenotype among dominants exposed to social isolation.

TH18. Cell-Type-Specific Dopamine Signaling in Ventral Hippocampus Tracks Anxiety-Related Behavior

Arthur Godino, Marine Salery, Angelica Minier Toribio, John Fullard, Eric Parise, Freddyson Martinez-Rivera, Carole Morel, Sarah Montgomery, Ming-Hu Han, Panagiotis Roussos, Eric Nestler*

Anxiety is an emotional response that, under normal conditions, promotes adaptive avoidance behaviors, but, when inappropriate to the level of threat, can contribute to

several psychiatric disorders. Despite accumulating evidence for a role of both the ventral hippocampus (vHipp) and the mesocorticolimbic dopamine system in encoding anxiety-relevant information, surprisingly little is known about how dopamine signaling selectively affects vHipp representations of emotionally-salient stimuli to guide innate approach/avoidance behaviors. To address these shortcomings, we here study dopaminoceptive neurons in mouse vHipp – which can be segregated based on their expression of either the dopamine D1 or D2 receptor – to delineate a model of dopamine action in vHipp. At the histological level, D1- and D2-expressing cells exhibit a precise topographical organization across vHipp subfields, which we further dissected using RNA-sequencing of single, sorted nuclei from D1- and D2-cells. Functionally, we showed that anxiogenic environments trigger distinct patterns of calcium activity in D1 and D2 cells, together with higher dopamine release in vHipp. Bidirectional chemogenetic and optogenetic manipulation of D1- or of D2-neurons' activity causally demonstrated their distinct roles in mediating anxiety and approach/avoidance behaviors. Intriguingly, cocaine exposure modified vHipp dopamine dynamics, with D1- and D2-expressing neurons differently modulating drug-related behaviors, suggesting drug-induced plastic changes in this circuit. Together, we propose that dopamine dynamics in vHipp operate as a feedback loop that bidirectionally tracks anxiety levels to gate exploratory behaviors through differential recruitment of vHipp D1- and D2-neurons, which in turn mediate opposite anxiety-like responses. This work paves the way for further studies of dopamine signal processing in limbic regions, and underscores the complexity of the circuit mechanisms that govern affective states.

TH19. Persistent Fluctuations in Striatal Acetylcholine and Dopamine Signaling: An Opportunity for Offline Learning?

Anne Krok, Pratik Mistry, Yulong Li, Nicolas Tritsch*

It is widely believed that there exists a steady state, basal tone of neuromodulators like acetylcholine (ACh) and dopamine (DA) that is periodically interrupted by phasic increases or decreases signaling salient events that need to be attended to, acted on or learned from. Here we employ a combination of techniques to simultaneously monitor cholinergic interneuron activity in vivo, as well as ACh and DA levels with dual color fiber photometry. We show that extracellular ACh levels in the dorsal striatum of mice constantly undergo large fluctuations several times a second, even during quiet wakefulness. We show that these fluctuations are driven by coordinated spiking of cholinergic interneurons. These fluctuations grow larger in amplitude during movement, in phase with acceleration, and are comparable in time course and magnitude to phasic ACh responses typically associated with reward. Importantly, these ACh fluctuations maintain a specific temporal relationship to striatal DA levels across behavioral contexts. These findings question the existence of a basal tone for ACh and DA, and suggest that phasic increases and decreases in ACh and DA are not uniquely associated with reward and salient behavioral events. Rather, our data indicate that striatal DA and ACh signaling is consistently and intrinsically structured, forcing a reconsideration of our understanding of modulation of neural activity and behavior by ACh and DA.

TH20. Striatal Dopamine Boosts Reinforcement Learning, Controlling for Effects on Working Memory and Cognitive Effort

Andrew Westbrook, Ruben van den Bosch, Lieke Hofmans, Danae Papadopetraki, Jessica Määttä, Michael Frank, Roshan Cools*

Stimulus-response learning can be accomplished entirely via incremental, dopamine-mediated reinforcement learning (RL). Yet, prefrontal cortex-based working memory (WM) may also contribute. Intuitively, WM affords rapid (e.g. one-trial) learning, but is limited in both capacity and the duration over which information can be maintained. WM is also effort-costly, and striatal dopamine signaling can promote willingness to do cognitive effort. Prior studies have failed to distinguish between the effects of dopamine on striatal RL or prefrontal WM contributions when observing that dopaminergic drugs speed learning. In this study, we test the hypotheses that striatal dopamine mediates both the degree to which people rely on costly working memory during stimulus-response learning and also RL speed, after taking into account WM contributions. N = 100 participants were recruited to complete a paradigm isolating WM contributions in a multi-session, double-blind, placebo-controlled, pharmaco-PET study in which we measure baseline dopamine synthesis capacity with [18F]DOPA, and separately manipulate dopamine with methylphenidate, and antagonize D2 receptors with sulpiride. As predicted, we find that striatal dopamine speeds learning. Specifically, both methylphenidate and higher dopamine synthesis capacity enhance learning, while sulpiride decreases accuracy. Computational modeling reveals that higher dopamine synthesis capacity predicts greater reliance on WM versus RL. Meanwhile methylphenidate boosts the rate of RL, controlling for its effects on WM. Consistent with our previous studies, we also find that methylphenidate diminishes effort discounting during reward learning. Finally, we find that accuracy was lower on sulpiride due to both diminished WM contributions to learning and also faster decay of WM contents.

TH21. Accumbal D1 and D2 Medium Spiny Neurons Have Distinct but Inter-Dependent Roles in Associative Learning

Jennifer Zachry, Munir Kutlu, Patrick Melugin, Kelly Shannon, Atagun Isiktas, Cody Siciliano, Erin Calipari*

The nucleus accumbens (NAc) is integrally involved in learning, selecting, and executing goal-oriented behaviors. These behaviors rely on associative learning processes, which is the ability to form associations between predictive cues and specific outcomes to support adaptive decision-making about future behavioral action. 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, in which D1 MSNs promote reward and D2 MSNs promote aversion. In this study, we aimed to define the precise information encoded within these neural populations during a series of behavioral tasks. First, 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. Next, in order 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 and single-photon cellular resolution calcium imaging to record from these cell populations in awake and behaving animals during Pavlovian and operant conditioning tasks. Our results show that D1 MSNs respond to the presence and intensity of unconditioned stimuli – regardless of value. We also found that D2- MSNs respond to learned associations. Finally, using optoenetics we found that D1 and D2 MSN inactivation during the outcome and predictive cue presentations, respectively, impaired fear learning suggesting that both of these processes are inter-dependent and critically involved in associative learning. Therefore, we concluded that the roles of D1- and D2-MSNs in associative learning differ but are not antagonistic, as current theories propose.

TH22. Activity Dynamics in the Central Nucleus of the Amygdala During Habit Formation

Kenneth Amaya, J. Eric Carmichael, Erica Townsend, Jensen Palmer, Kyle Smith*

Habits are behaviors that are notoriously automatic, consistent, and inflexible and emerge with repeated performance of an action. Neural recordings of key habit areas like the infralimbic cortex, dorsolateral striatum (DLS), and substantia nigra have previously characterized activity dynamics while a habit was formed and executed. Meanwhile, as the central nucleus of the amygdala (CeA) has been extensively studied with respect to threat learning, a smaller body of literature has implicated this amygdalar nucleus as being involved in appetitive conditioning as well. In particular, the CeA has been shown to be necessary for the development of instrumental habit behaviors. Additionally, although there are no known direct projections between the two areas, contralaterally lesioning DLS and CeA similarly abolishes habit formation, further solidifying the idea that the CeA is involved in habit formation. To formally address this, we trained animals on an elevated plus-maze task that consistently required a specific response to earn rewards and quantified c-Fos expression in CeA. In the next experiment, we implanted animals with silicon probes targeting the CeA and recorded neural activity throughout training and during post-outcome-devaluation extinction and reacquisition sessions. In sum, our findings reflect that CeA neurons were recruited during habit formation (as evidenced by c-Fos expression) and the neural activity recorded appeared to be dynamic as training progressed to accentuate pre- and post-reward delivery late in training.

TH23. Dynorphinergic Control of Amygdalo-Striatal Circuits for Goal-Directed Action

Raajaram Gowrishankar, Abigail Elerding, Sofia Shirley, Sean Piantadosi, Adam Gordon-Fennell, Charles Zhou, David Marcus, Kat Motovilov, Garret Stuber, Michael Bruchas*

Elegant work spanning decades has implicated the dorsomedial striatum (DMS) in how animals learn, perform and update goal-directed actions. Yet, the circuit- and molecular-level substrates involved in these behaviors remain largely unknown. Given its role in encoding valence, neural projections from the basolateral amygdala (BLA) to the DMS are

uniquely poised to sculpt action-outcome behaviors. ~50% of the neurons in the DMS express dynorphin; although how dynorphin (dyn) coordinates these strategies is yet to be elucidated. Interestingly, ours and prior studies have shown that BLA neurons project preferentially to DMS dyn neurons and that DMS-projecting BLA neurons express kappa-opioid receptors (KOR). Hence, we hypothesize that BLA projections to the DMS coordinate outcome-based action, under the control of dyn-KOR signaling. Here, we show that retrograde dyn transmission at BLA terminals in the DMS inhibits BLA-DMS activity during outcome delivery, refines increased activity during action, and promotes action-outcome behaviors for natural reward. Using fiber photometry in BLA terminals expressing GcaMP6s in the DMS, we show that BLA terminals are active during action and inhibited during outcome. We also observe that BLA-DMS activity changes dynamically and reversibly to manipulations in outcome-probability or outcome-value. Notably, we find that this engagement is sensitive to disruptions in dynorphinergic signaling via naloxone or through local deletion of dyn in the DMS, or KOR in the BLA. Using a novel dyn sensor, we observe that DMS dyn is released during reward retrieval, suggesting that dyn release and subsequent KOR signaling inhibits BLA-DMS activity during outcome. In parallel, using time-locked optogenetic manipulations of BLA-DMS terminals, we find that photoactivation during outcome disrupts action and conversely, photoinhibition enhances actions. Collectively, our data suggest that BLA-DMS activity informs outcome-dependent action and is regulated by dyn-KOR signaling at these terminals during outcome. Current work is focused on delineating how BLA-DMS axons differentially engender action or outcome using in-vivo 2-photon Ca2+ imaging of DMS-projecting BLA neurons or BLA axon clusters in the DMS during a novel, head-fixed operant task.

TH24. Activation of S1PR1 Signaling in the CNS Drives Cisplatin-Induced Cognitive Impairment

Silvia Squillace, Michael Niehoff, Timothy Doyle, Michael Green, Salvatore Cuzzocrea, Christopher Arnatt, Sarah Spiegel, Susan Farr, Daniela Salvemini*

Chemotherapy-induced cognitive impairment (CICI) is a major neurotoxicity affecting >50% of cancer survivors. Underpinning mechanisms are mostly unknown, and there are no FDA-approved interventions. We showed that cisplatin increased sphingosine-1-phosphate (S1P) in mouse prefrontal cortex and hippocampus and led to significant cognitive impairment. The molecular mechanisms whereby cisplatin increase S1P production are not known but our pharmacological and genetic approaches coupled with computational modeling studies implicate toll-like receptor 4. At the biochemical level, increased formation of S1P was associated with nitration and inactivation of mitochondrial superoxide dismutase (MnSOD), activation of NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome, and inflammatory cytokines production. These findings implicate S1PR1 induced mitochondrial dysfunction and neuroinflammation as important contributors to CICI. Noteworthy, systemic administration of the S1P-receptor-1 (S1PR1) functional antagonist FTY720 (fingolimod) prevented MnSOD nitration/inactivation and NLRP3 activation, and significantly attenuated CICI without adversely affect locomotor activity. Beneficial effects on CICI were extended to another functional S1PR1 antagonist,

ozanimod (RPC1063/Zeposia®). Our results provide new insight into the mechanism of CICI by establishing the specific role of S1P/S1PR1 and identify S1PR1 as a target for therapeutic intervention with S1PR1 antagonists. Repurposing these drugs to treat CICI would be a ground-breaking shift towards emphasizing patient quality of life in cancer treatment.

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TH25. The Relationship Between Free Triiodothyronine (FT3) and Performance on the Iowa Gambling Task in Bipolar Disorder: Sex Differences Explored

Caitlin Millett, Meg Shanahan, Katherine Burdick*

Introduction: Thyroid dysfunction has been implicated in the pathophysiology of bipolar disorder (BD) because of the known effects on cognition and mood. Here we aimed to examine the effect of thyroid hormones and behavior on a reward learning paradigm, the Iowa Gambling Task (IGT).

Methods: The study included 101 males and 94 females with a diagnosis of BD. BD diagnosis was confirmed by the structured clinical interview based on the DSM-IV (SCID-IV). For both males and females, we performed a repeated-measures analysis of covariance (RM ANCOVA) with five blocks of the IGT as the within-subjects factor, free triiodothyronine (FT3) high-versus-low median split as the between-subjects factor, and age in years as a covariate. To assess the associations between three expectancy valence (EV) measures (consistency, attention to losses, and recency) and FT3, we performed partial Pearson correlations controlled for age.

Results: We observed a significant interaction between FT3 and IGT blocks in males with BD ($F(4,95)=2.9$, $p=0.02$), but not in females with BD ($F(4,88)=0.2$, $p=0.9$). For males, those in the low FT3 group appeared to have a more gradual and normal learning curve compared to those in the high FT3 group. In terms of learning strategies, we observed a significant negative correlation between FT3 and consistency in males ($R= -0.3$, $p=0.001$), indicating that they employ a more exploratory approach in association with higher FT3. We did not observe this relationship in the females ($R= -0.03$, $p=0.7$). We did not find significant associations in any of the other EV measures.

Conclusions: We observed differential emotional learning styles in males with high versus low FT3 in the IGT. These results suggest a role of the thyroid in emotional learning and exploratory behaviors in males with BD.

TH26. Spatially-Restricted Dopamine Signals Evoke Post-Synaptic Responses in Striatal Neurons

Andrew Yee, Chris Ford*

Dopamine (DA) signaling is commonly thought to be mediated by volume transmission, whereby low concentrations of the transmitter non-selectively activate non-synaptic DA receptors after its diffusion from distant release sites. However, recent evidence has indicated that high concentrations of DA are released from sparse hotspots which comprise

only a small proportion of striatal DA varicosities. Until now, existing tools have limited our ability to resolve the spatial and concentration dynamics of DA signaling. Using a combination of two-photon imaging of a genetically-encoded DA sensor (dLight1.3b) and electrophysiology to measure post-synaptic responses in striatal indirect-pathway spiny projection neurons (iSPNs), we have spatially and temporally quantified electrically-stimulated DA release, and directly correlated these signals with post-synaptic responses. These responses could be reproduced by focal application of a high, but not a low concentration of exogenous DA, confirming that receptor activation requires high concentrations of DA. Localized stimulation of only a few DA release sites (within 2-3 µm), evoked spatially-restricted DA release which produced post-synaptic responses depending on overlap between dLight fluorescence and the dendrites of iSPNs. Taken together, these data suggest that tight organization between DA release sites and the dendrites of iSPNs shapes post-synaptic responses, challenging the idea that DA signaling is only mediated by volume transmission.

TH27. Regulation of Kölliker-Fuse Neurons by Co-Release of Noradrenaline and Glutamate From the Locus Coeruleus

Adrienn Varga, Sebastian Maletz, Amanda Dossat, Brandon Reid, Erica Levitt*

The primary cause of death from opioid overdose is respiratory depression, mediated by mu-opioid-receptors in respiratory control regions of the brain. The sedative effect of opioids further impairs respiratory drive through largely unexplored mechanisms. The pontine respiratory center, Kölliker-Fuse nucleus (KF), is highly susceptible to inhibition by opioids, significantly contributing to opioid-induced respiratory rate and pattern changes. Utilizing cell-type specific retrograde neural tracing, we characterized anatomical projections between the main noradrenergic arousal/wakefulness center of the brain, the locus coeruleus (LC), and the KF, which represent a potential link between arousal/sedation and respiratory control. We found that on average 30% of noradrenergic LC neurons send projections to the KF. To explore the functional role and neurochemical identity of LC to KF projections, we used whole-cell patch clamp recordings combined with optogenetic stimulation of LC neurons. Optical stimulation of LC axon terminals induced light-evoked glutamatergic excitatory postsynaptic currents in KF neurons. Pharmacological isolation of LC to KF synapses indicates that this pathway is monosynaptic. These glutamatergic excitatory postsynaptic currents were dependent on vesicular glutamate transporter 2 expression in noradrenergic LC neurons. In addition, longer optical stimulations resulted in noradrenergic excitatory postsynaptic currents that were blocked by alpha1 receptor antagonist. Thus, LC may drive KF neuron activity via glutamate and/or noradrenaline release. This direct excitatory drive in the LC-KF circuit is sensitive to opioids, which can directly inhibit KF neuron somas, as well as inhibit neurotransmitter release from presynaptic LC terminals. This work provides exciting novel evidence for an excitatory pathway between the LC and the pontine respiratory center KF, that may play an important link between opioid-induced sedation and respiratory depression.

TH28. Striatal Fiber Photometry Reflects Primarily Non-Somatic Activity

Alex Legaria, Ben Yang, Julia Licholai, Biafra Ahanonu, Jones Parker, Alexxai Kravitz*

Calcium recording via fiber photometry is commonly used as a proxy for recording population neuronal activity in vivo, yet the biological source of the photometry signal remains unclear. Here, we first tested whether the calcium fiber photometry signal correlates well with spiking activity by performing simultaneous in vivo extracellular electrophysiology and fiber photometry in the striatum. We observed only a moderate correlation between calcium transient size and the size of change in spiking activity. To test whether photometry signal primary source comes from non-somatic calcium activity, we performed endoscopic 1-photon, and 2-photon calcium imaging, and tested whether the photometry signal had a better correlation with non-somatic changes in calcium than with somatic changes in calcium. We observed almost a perfect correlation between calcium changes in non-somatic regions of the imaging field and the photometry signal. We conclude that calcium fiber photometry signal reflects primarily changes in non-somatic calcium.

TH29. Somatodendritic Release of Cholecystokinin Modulates Ventral Tegmental Area GABAergic Plasticity

Valentina Martinez Damonte, Matthew B. Pomrenze, Caroline Casper, Yihe Ma, Huan Wang, Yulong Li, Robert C. Malenka, Julie A. Kauer*

Most dopamine (DA) neurons express the neuropeptide cholecystokinin (CCK), but to date its role in ventral tegmental area (VTA) circuitry has remained elusive. In electrophysiological recordings in horizontal midbrain slices, we recently found that VTA DA neuron depolarization triggers the somatodendritic release of CCK, which in turn potentiates GABAergic transmission onto DA neurons. Here we explore CCK release and its impact on VTA-related behaviors.

First, we examined the mechanisms underlying CCK release. Since depolarization of DA neurons releases CCK, we tested whether optogenetic activation of DA neurons alone might release CCK. Our preliminary data ELISA results confirm this, and furthermore, this maneuver also potentiated IPSCs in DA cells. We are also setting up an assay with a GRABCCK sensor to confirm this. As Ca2+ chelation prevents CCK-induced LTP, we next evaluated if blocking T-type voltage-gated calcium channels prevents depolarization-induced LTP and found that depolarization could not elicit potentiation of GABAergic synapses in the presence of NiCl2 (50µM). We are currently evaluating the involvement of other cellular proteins that may be required to support CCK release.

We then tested whether CCK could modulate DA cell activity in vivo. The ability of CCK to modulate DA neuron excitability may have important implications for reward behavior. We found that in fasted mice intra-VTA CCK delivery decreases consumption of food, a natural reward. However, we also observed in an open field test that CCK delivery decreased the total distance traveled and time spent in the field center, suggesting that locomotor deficits or anxiety could contribute to the food intake results.

Our work in VTA DA neurons reveals a novel role for CCK somatodendritic release as an novel modulator of the local circuit and its behavioral consequences.

TH30. Tam Receptors are Modulators of Pathology in Amyotrophic Lateral Sclerosis

Youtong Huang, Patrick Burrola, Greg Lemke*

Amyotrophic Lateral Sclerosis (ALS) is an irreversible and uniformly fatal neurodegenerative disease characterized by selective degeneration of motor neurons (MNs) and progressive muscle dystrophy that is accompanied by chronic neuroinflammation. Reactive microglia are thought to play crucial roles in ALS pathogenesis by mediating the death of MNs and the secretion of pro-inflammatory agents. These cells, among all tissue resident macrophages, express the TAM receptor tyrosine kinases Mer (gene: Mertk) and Axl. Our lab and others have previously demonstrated important roles of TAM receptors in microglia and other immune sentinels, including the phagocytic clearance of apoptotic cells and the feedback inhibition of the innate immune response. Recent transcriptomic evidence identifies Axl as a signature 'disease-associated microglia' gene in the SOD1G93A mouse model of ALS. These findings notwithstanding, whether and how microglial TAM receptors participate in ALS disease progression has not been experimentally addressed. We found a persistent up-regulation of both microglial Mer and Axl, as well as their ligand, in the SOD1G93A spinal cord beginning at symptomatic onset, suggesting a strong activation of the TAM signaling pathway throughout disease. Interestingly, SOD1G93A mice in the absence of Axl and Mer have significantly advanced symptom onset, but their disease course is almost twice the length of that of TAM-expressing SOD1G93A mice. We showed this delayed arrival of end-stage of disease may be accompanied by dampened microglial activation and reduction in the loss of ALS-vulnerable MNs in the spinal cord, as well as a partial rescue of neuromuscular junction loss and preservation of muscle fiber in the skeletal muscle that may be mediated by TAM deficiency in muscle-resident macrophages. Our work demonstrates a critical and differential involvement of TAM receptors in early and late stages of ALS in both the central and periphery nervous system. Given that TAM inhibitors are already in clinical trials as cancer therapeutics, discoveries from our studies will not only further our understanding of how the innate immune system mediate ALS pathology through TAM signaling, but may potentially be translated into novel therapeutic targets for the treatment for ALS and other neurodegenerative diseases.

TH31. High Fat Diet Feeding Disrupts Thermal Responsiveness of AgRP Neurons

Jennifer Deem, Tammy Doan, Bao Anh Phan, Kayoko Ogimoto, Shannon Hu, Hamza Hussain, Padma Gundapaneni, Michael Schwartz, Gregory Morton*

To defend energy homeostasis in the cold requires energy expenditure (to support thermogenesis) and energy intake increase, enabling core temperature to be maintained with no change to body fat stores. When acutely housed at a mild cold (14°C), mice increase both food intake and heat production rapidly (~minutes), and these responses occur in parallel. We hypothesized a role for Agouti-related peptide (AgRP) neurons in this

response and find their activity is regulated by thermal sensory input, and they increase activity, measured by Fos induction and fiber photometry, upon cold sensation, and reduce activity as sensed temperatures rise. By inhibiting AgRP neurons during acute cold exposure, we also find this increase in AgRP neuron activity is required for the hyperphagic response to cold. Recent evidence found high-fat diet (HFD) feeding reduced AgRP neuron responsiveness to gastric hormones and standard chow diet presentation, and we hypothesized that their response to thermal input might also be blunted. We find that although 12-week HFD-fed mice exhibit intact thermogenic responses to cold and defend a normal core body temperature, they fail to increase energy intake and consequently experience weight loss not observed in chow-fed controls. This uncoupling of energy intake from energy expenditure is present even after a shorter, 2-week exposure to HFD-feeding, implying a role for diet separate from obesity in the phenotype. Using Agrp-Cre/GFP marker mice, we find acute cold exposure rapidly induces Fos in chow-fed mice, but this response is lacking in HFD-fed mice. This effect correlates with a failure to increase hypothalamic Agrp mRNA even after five days of mild cold exposure. Using photometry to measure AgRP neuron calcium activity, we find activity changes associated with thermal input, both cold and warm, are blunted with HFD feeding.

TH32. A Novel Intersectional Tool to Study Locus Coeruleus Subpopulations

Alex Hughes, Gabrielle Pollard, Lindsay Schwarz*

Advances in genetic profiling have furthered our understanding of the neuronal subpopulations present in the brain. As more specific classifications grow, so too does our need to target these unique populations selectively. Current intersectional strategies target these subpopulations by utilizing viral constructs to deliver a payload that is expressed after subsequent recombination events mediated by different recombinases (i.e., Cre and Flp). However, these targeting approaches often require multiple viral constructs, bulky silencing regions, or complex cloning strategies, thus limiting their use and adaptability. I have developed a novel, single-construct intersectional targeting strategy that is easily customizable and allows for the delivery of large payloads. I will use this ConVERGD (Conditional Viral Expression by Ribozyme Guided Degradation) strategy to target specific neurons within the locus coeruleus (LC). As the primary source of NE for the adult brain, the LC is a major regulator of diverse arousal states. Less known is how the genetic diversity of the LC neurons contributes to this regulation. Presently, I have used ConVERGD constructs to target a novel subpopulation of LC neurons producing both NE and the stress-related endogenous opioid dynorphin (Dyn). These studies showcase ConVERGD as a versatile tool capable of targeting genetic subpopulations of neurons and reveal Dyn+/NE+ LC neurons as a clinically relevant neuronal population that drives an anxiogenic behavioral response.

TH33. Integrated Analytic and Machine Learning Framework to Leverage Electrophysiology Datasets in the Data Archive for the Brain Initiative

Rachael Garner, Faraz Rabbini, Samuel Hobel, John Magnotti, Zhengjia Wang, Michael Beauchamp, Nader Pouratian, Arthur W. Toga, Dominique Duncan*

The Data Archive for the BRAIN Initiative (DABI) fills the need for a centralized repository for intracranial electrophysiology. DABI has aggregated imaging, neurophysiology, and clinical data for 535 subjects recruited through 24 BRAIN Initiative-affiliated institutions. As adoption of standardized data specifications is ongoing, DABI recently led curation efforts to enable multi-site investigations. Standardized metadata fields were translated into the data-interchange format JavaScript Object Notation (JSON), a primary data structure utilized by Brain Imaging Data Structure-Intracranial Electroencephalography (BIDS-iEEG).

Despite these harmonization efforts, analysis of chronic recording is still a challenge due to noise artifacts, a lack of validated event detection algorithms optimized for naturalistic recordings, and technical burdens of managing and processing continuous temporal data. Therefore, DABI has built an analytic workflow to leverage these curated, large-scale datasets. Intracranial electroencephalography (iEEG) can first be processed on DABI servers through R Analysis and Visualization of intracranial EEG (RAVE), which supports customizable preprocessing, analysis, and visualization. RAVE outputs, including power spectrum analyses, can then be introduced alongside clinical variables in DABI's AutoML pipeline, a machine learning system that facilitates supervised data exploration and event detection. AutoML includes supervised learning to perform classification and regression with standard algorithms in the H2O library (R and Python supported), including General Linear Model, Random Forest, XGBOOST, Gradient Boosting Machine, and Deep Learning. DABI's AutoML pipeline is designed to support users from a variety of backgrounds by reducing programmatic barriers to model building: users can build models within minutes by inputting only specific parameters, such as the number of folds for k-fold cross-validation or whether to perform oversampling to balance an unbalanced dataset. Users can immediately evaluate model performance through visualized results, including variable importance and area under the curve performance.

TH34. Opioid Inhibition of Projection-Specific, Respiratory-Related Pontomedullary Neurons

Jordan Bateman, Erica Levitt*

Opioids depress breathing by inhibition of inter-connected respiratory nuclei in the pons and medulla. We have previously shown that mu opioid receptor (MOR) agonists hyperpolarize a population of neurons in the dorsolateral pons due to activation of G protein-mediated inwardly rectifying potassium conductance. However, we do not know the projection target of MOR-expressing, dorsolateral pontine neurons, if they project at all. Here, we show that MOR-expressing, dorsolateral pontine neurons project to core respiratory nuclei in the ventrolateral medulla, identifying projection-related heterogeneity

of dorsolateral pontine neurons vulnerable to opioid inhibition. First, retrograde DIO-eGFP injections into the ventrolateral medulla of oprm1-cre mice showed that dorsolateral pontine neurons project to the Bötzinger complex (BötC), pre-Bötzinger complex (preBötC), and rostral ventral respiratory group (rVRG), and are distinct from calcitonin gene-related peptide (CGRP)-expressing parabrachial neurons. Second, we performed whole-cell, voltage-clamp recordings from dorsolateral pontine Kölliker-Fuse neurons that were retrogradely labeled by fluorescent bead injections into the ventrolateral medulla of wild-type mice. MOR-mediated outward currents were identified in dorsolateral pontine neurons that project to the BötC, preBötC, and rVRG, confirming that these projection neurons are functionally inhibited by MORs and vulnerable to opioid inhibition. Together, these approaches demonstrate that MOR-expressing, dorsolateral pontine neurons project to medullary respiratory nuclei and further unravel mechanisms of opioid-induced respiratory depression.

TH35. Functional Connectivity Correlated to Rapid Remission to Intermittent Theta-Burst Stimulation (aiTBS) Therapy for Severe Major Depressive Disorder: Results From a Randomized Controlled Clinical Trial

Azeezat Azeez, Xiaoqian Xiao, Jean-Marie Batail, Nolan Williams*

Advances in neuroimaging have improved our understanding of the neural circuitry underlying mood disorders and have helped guide neuromodulation treatments such as Transcranial Magnetic Stimulation (TMS). These trends in combination with the described double-blinded randomized control trial, place us in a unique position to expand our understanding of the neural mechanism of depression and modulatory effects, observed as changes in clinical outcome, to a novel TMS intervention.

We report 24 participants with treatment-resistant Depression who underwent a 5-day course of high dose accelerated intermittent theta-burst stimulation(aiTBS). The personalized stimulation target was derived from baseline functional connectivity (FC) anticorrelation between subgenual cortex(sgACC) and lDLPFC. We studied resting-state fMRI markers of 1-week and 1-month treatment outcomes after aiTBS intervention.

A whole-brain analysis exhibited significant interaction between active and sham groups of both baseline FC's and FC changes (all p's < 0.01, all power > 0.6) associated with clinical treatment effects. Networks/regions involved in emotional reactivity (amygdala and striatum), explicit control of emotion (CEN and DAN), implicit emotion regulation(DMN, salience affective network, and insula), learning and emotion processing brain regions(hippocampus and thalamus) were significantly altered.

An exploratory analysis of sgACC and target seeds revealed that, compared to the sham group, greater sgACC-DMN baseline FC was correlated to better clinical outcomes in the active group($t(20)=-3.688$, $p=0.001$; uncorr). The opposite trend was found in baseline FC between target-DMN($t(20)=2.627$, $p=0.016$; uncorr). Moreover, we also found that a greater increase of target-DMN FC was associated with better clinical outcomes($t(20)=-2.319$, $p=0.032$; uncorr)

Overall this study brings new evidence of functional brain changes of the rapid-acting antidepressant effect of high dose, fMRI guided, aiTBS treatment.

TH36. An Optogenetic Stimulation-Based Model of Inflammatory Injury Persistently Enhances the Excitability of Spinal Neurons Targeting the Periaqueductal Gray

Chelsie Brewer, Julie A. Kauer*

A model of inflammatory injury, high-intensity stimulation of peripheral somatosensory neurons at 2 Hz for 2 minutes (LFS), selectively potentiates excitatory synapses onto a small population of spinal projection neurons targeting the periaqueductal gray (PAG), a region critical to pain processing. However, given the vast diversity of dorsal root ganglion neurons and the gap in knowledge on the output of spino-PAG projection neurons after potentiation, we sought to identify the afferent population underlying this potentiation and how this enhanced synaptic drive may affect supraspinal pain circuits. We isolated C fibers, which have high activation thresholds and are associated with nociception, using a genetic mouse model expressing channelrhodopsin driven by the TRPV1 gene, which codes for the canonical capsaicin receptor. We injected diI into the PAG to retrogradely label spinal projection neurons for whole-cell patch-clamp recordings in an intact spinal cord preparation. A single optical activation of TRPV1-expressing (TRPV1+) peripheral afferents induced a burst firing in most spino-PAG projection neurons, and LFS persistently increased the number of intraburst APs ($n=10$, $p=0.029$). Further analysis revealed an initial transient membrane depolarization during the LFS protocol (Mean=6.796 mV, $n=12$, $p<0.0001$) and a lasting decrease in the afterhyperpolarization of APs within a burst ($n=10$, $p=0.037$). Additional experiments suggested that these effects were dependent on postsynaptic G protein-coupled signaling, NMDA receptors, and synaptic input from TRPV1+ afferents. Furthermore, LFS altered the intrinsic properties of spino-PAG neurons—increasing membrane resistance ($n=14$, $p=0.0003$) and decreasing intracellular current-evoked AP threshold ($n=14$, $p=0.015$). In summary, this work suggests that TRPV1+ fiber LFS persistently enhances the output of spino-PAG projection neurons, presumably leading to a lasting increase in supraspinal activation of PAG neurocircuits.

TH37. Neural Basis of Opioid-Induced Respiratory Depression and Its Rescue

Shijia Liu, Dongil Kim, Tae Gyu Oh, Gerald Pao, Jonghyun Kim, Richard Palmiter, Matthew Banghart, Kuo-Fen Lee, Ronald Evans, Sung Han*

Opioid-induced respiratory depression (OIRD) causes death following an opioid overdose, yet the neurobiological mechanisms of this process are not well understood. Here, we show that neurons within the lateral parabrachial nucleus that express the μ-opioid receptor (PBLOprm1 neurons) are involved in OIRD pathogenesis. PBLOprm1 neuronal activity is tightly correlated with respiratory rate, and this correlation is abolished following morphine injection. Chemogenetic inactivation of PBLOprm1 neurons mimics OIRD in mice, whereas their chemogenetic activation following morphine injection rescues respiratory rhythms to baseline levels. We identified several excitatory G-protein coupled receptors expressed by PBLOprm1 neurons and show that agonists for these receptors restore breathing rates in mice experiencing OIRD. Thus, PBLOprm1 neurons are critical for OIRD pathogenesis, providing a promising therapeutic target for treating OIRD in patients.

TH38. Subcellular Localization of Schizophrenia Risk Genes Encoding Cav1.2 (CACNA1C) and VIPR2 in Rhesus Macaque Dorsolateral Prefrontal Cortex

Dibyadeep Datta, SueAnn Mentone, Yury Morozov, Amy Arnsten*

Background: The dorsolateral prefrontal cortex (dlPFC) mediates high-order cognition, and is profoundly afflicted in schizophrenia, including dendritic spine loss from deep layer III, the circuits that generate persistent firing needed for working memory. Studies in monkeys show that these dendritic spines contain the molecular machinery for cAMP to magnify internal calcium release, where moderate levels sustain neuronal firing, but high levels weaken connectivity via opening nearby potassium channels. Genetic studies have linked schizophrenia risk with gain of function alterations in the Cav1.2 calcium channel encoded by CACNA1C, and a duplication in VIPR2, which increases cAMP intracellular signaling. The current research examined the localization of these key signaling proteins in layer III of the rhesus monkey dlPFC.

Methods: Using high-spatial resolution immunoelectron microscopy coupled with immunoperoxidase immunocytochemistry, we interrogated the subcellular localization of 1) L-type voltage-gated calcium channel Cav1.2, and 2) Gs-protein coupled receptor VIPR2, in dlPFC layer III in middle aged monkeys.

Results: We found significant labeling of VIPR2 and Cav1.2 in dlPFC layer III dendritic spines. VIPR2 and Cav1.2 were predominantly localized in perisynaptic or extrasynaptic compartments on the plasma membrane near glutamatergic asymmetric axospinous synapses, often in association with the calcium-storing smooth endoplasmic reticulum (SER) spine apparatus, positioned to modulate intracellular calcium within nanodomains. We also observed direct association of VIPR2 and Cav1.2 with the post-synaptic density in the synaptic active zone, localized in subcompartments required to depolarize the membrane.

Discussion: Cav1.2 and VIPR2 are positioned to drive calcium influx and cAMP signaling in layer III dlPFC spines, respectively. As both cAMP and Cav1.2 increase calcium efflux from internal SER stores, gain of function mutations in these signaling proteins in schizophrenia may lead to excessive calcium signaling, which may contribute to dendritic spine loss and cognitive deficits.

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