Alcoholism and Stress: A Framework for Future Treatment Strategies

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May 12-15, 2026

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Mateo Leganes-Fonteneau

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Bach, Patrick
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P142 Insular stress ensembles are directly recruited during ethanol consumption, neurobiologically linking traumatic stress and AUD-related behavior
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Victor Schneider

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P147 External Globus Pallidus Arkypallidal Circuit Dynamics Gate Risk-Taking Behavior
David Haggerty

PROGRAM

Tuesday, May 12, 2026

8:00 a.m. – 8:15 a.m. **Introduction**
Marisa Roberto

8:15 a.m. – 9:00 a.m. **Plenary Lecture**
PL1 Bringing back the light! Restoring hijacked alcohol motivation and adaptive stress responses from the dark side.
Rajita Sinha, Ph.D., Professor, Yale Stress Center, Yale University School of Medicine, New Haven, CT USA

9:00 a.m. – 10:30 a.m. **Symposium I**
The interface of Stress, Alcohol and Endocannabinoids: A Memorial Session for Larry Parsons
Chair: Matthew Hill

S3 Stress Differentially Regulates Discrete Projection Populations from the Basolateral Amygdala
Matthew Hill

S4 Interactions between acute alcohol consumption and peripheral endocannabinoids on brain and behavioral correlates of reward and threat responding in humans
Leah Mayo

S5 Cannabinoid Modulation of Central Amygdala Population Dynamics During Threat Investigation
Sachin Patel

S6 Endocannabinoid mediated frontal cortical control in adaptive stress coping and subsequent alcohol drinking
Laura Ornelas

10:30 a.m. – 11:00 a.m. **Coffee Break**

11:00 a.m. – 12:30 p.m. **Symposium II**
Converging mechanisms of pain, anhedonia and alcohol use disorders
Chair: Lucia Hipolito

S7 Crosstalk of the opioid receptors and neuroinflammation: role in pain, anhedonia and alcohol intake in rats
Lucia Hipolito

S8 Non-synaptic basis of addiction: translational MRI evidence in alcohol use disorders
Santiago Canals

S9 CeA-v1PAG Circuit Regulation of Adolescent Alcohol-induced Hyperalgesia
Tiffany Wills

S10 Role of a dynorphinergic CeA to BNST input in pain-induced anhedonia
Jose Moron-Concepcion

12:30 p.m. – 1:30 p.m. **Light Refreshments**

1:30 p.m. – 3:00 p.m. **Symposium III**
Caught in the Middle: Midline Thalamic Mechanisms of Vulnerability to Stress and Alcohol
Chairs: Kristen Pleil and Jennifer Rinker
Discussant: David Lovinger

S11 Alcohol dependence disrupts stress-sensitive thalamic inputs onto accumbal parvalbumin interneurons to promote alcohol seeking
Jennifer Rinker

S12 Substance P projections from the paraventricular nucleus of the thalamus to the nucleus accumbens and central amygdala: a potential mediator of alcohol consumption following social defeat stress
Lauren Beugelsdyk

S13 Alcohol dysregulation of adaptive estrogen signaling in the limbic thalamus
Kristen Pleil

S14 Genetic and physiological adaptations in the nucleus reuniens of the thalamus as drivers of aberrant alcohol- and stress-related behaviors in mice
Patrick Mulholland

S15 Frontocortical thalamic inputs are selectively vulnerable to adolescent alcohol consumption in a mouse model of ADHD
Michael Salling

1:30 p.m. – 3:00 p.m.

Symposium IV
Effects of ethanol and its metabolites on genes, ion channels, and bioenergetics: from molecular to organismal perspective
Chairs: Paul Slesinger and Alex Dopico

S16 Why Some Resist: Epigenetic Control of Resilience to Compulsive Alcohol Drinking
Daniel da Silva

S17 Selective activation of GIRK1 potassium channels reduces behavioral and brain responses to ethanol in mice
Paul Slesinger

S18 Reduced Ethanol Drinking and Glycine Receptor Function in the Nucleus Accumbens with Age.
Luis Aguayo

S19 Cerebral artery smooth muscle BK channels are functional targets of ethanol and the neurosteroids pregnenolone and progesterone
Alex Dopico

3:00 p.m. – 4:30 p.m.

Symposium V
Insular dynamics in stress and alcohol use: a cross-species perspective on craving, compulsion, and abstinence
Chair: Samuel Centanni
Discussant: Elizabeth Goldfarb

S20 Stress-induced sensitization of insula activation predicts alcohol craving and alcohol use in alcohol use disorder
Patrick Bach

S21 The insular cortex: the gateway from impulses to compulsion
David Belin

S22 The distinct roles of the S1-insula circuit in alcohol drinking and stress-evoked behavior in abstinence
Samuel Centanni

S23 Sex differences in incubation of craving for alcohol-associated cues: a role for the insular cortex
Christina Perry

4:30 p.m. – 5:30 p.m. **Poster Session and Snacks**

Wednesday, May 13, 2026

8:00 a.m. - 9:45 a.m.

Symposium VI
Dynorphinergic / kappa-opioid receptor-regulated cortical and limbic circuitry at the intersection of alcohol and stress
Chairs: Brendan Walker and Ethan Anderson
Discussant: Rainer Spanagel

S24 Adolescent social isolation enhances stress and alcohol vulnerability via opioid gene expression changes in a sex-dependent manner
Esi Domi

S25 Kappa opioid receptor modulation of BLA inputs to the BNST regulates social stress escalated alcohol intake
Rajani Maiya

S26 Corticolimbic dynorphinergic / kappa-opioid receptor circuitry underlies dysphoria cue-induced escalation of alcohol self-administration
Brendan Walker

S27 Prefrontal cortex bidirectionally routes stimulus valence to the periaqueductal gray via glutamatergic and dynorphinergic mechanisms
Cody Siciliano

S28 A Methyltransferase Knockdown in the Accumbens Increases Excitability and Reduces Stress-Escalated Ethanol Drinking in Mice
Ethan Anderson

9:45 a.m. – 10:15 a.m. **Coffee Break**

10:15 a.m. – 12:15 p.m.

Clinical Trial Roundtable
Chairs: Katie Witkiewitz, Ph.D., Professor, University of New Mexico, Albuquerque, NM, USA
Carolina Haass-Koffler, Ph.D., Associate Professor, Brown University, Providence, RI, USA

R29 Clinical Trial Roundtable
Mack Mitchell, M.D., Prof. of Internal Medicine, Univ. of Texas Southwestern Medical Center, Dallas, TX, USA
Patrick Bach, M.D., Ph.D., Professor, Central Institute of Mental Health, Mannheim, Germany
Christy Capone, Ph.D., and Erica Eaton, Ph.D., Assistant Professors, Brown University, Providence, RI, USA
Anne Fernandez, Ph.D., Associate Professor, University of Michigan Medical School, Ann Arbor, MI, USA
Roberta Agabio, M.D., Professor, Department of Biomedical Sciences, University of Cagliari, Italy
Markus Heilig, M.D., Ph.D., Professor of Psychiatry, Linkoping University, Sweden

12:15 p.m. – 1:15 p.m. **Light Refreshments**

1:15 p.m. – 2:45 p.m. **Symposium VII**
Modulating central cholinergic activity: implications for therapeutic potential in treatment of alcohol and stress related disorders
Chairs: Howard Becker and Andrew Lawrence

S30 Neurotoxic effects of chronic ethanol on cholinergic interneurons in the dorsomedial striatum
Armando Salinas

S31 Adolescent intermittent Ethanol Exposure Disrupts Neurotrophin Balance to Drive Cholinergic and Behavioral Dysfunction
Lisa Savage

S32 Muscarinic M4 & M1/M4 Receptor Agonists for Schizophrenia, Historical Perspective & Current Status with implications for the treatment of alcohol use disorder.
Anders Fink-Jensen

S33 M4 Muscarinic Acetylcholine Receptor Agonism Decreases Alcohol Drinking and Stress-Induced Alcohol Relapse in Mice
Howard Becker

1:15 p.m. – 2:45 p.m. **Symposium VIII**
Recent Advances in Animal Models of Alcohol Consumption Despite Negative Consequences
Chair: Jesse Schank

S34 Unveiling Genetic Determinants of Alcohol Addiction Vulnerability: Insights from Genetically Diverse Rat Models
Giordano de Guglielmo

S35 Transcriptomic analysis of the central amygdala in aversion-resistant alcohol use: Sex differences
Leon Hoglund

S36 Social isolation following alcohol consumption suppresses subsequent intake in mice
Jesse Schank

S37 Exploring the neural mechanisms underlying addiction using improved models of aversion resistance
Elizabeth Glover

2:45 p.m. – 4:30 p.m. **Symposium IX Honoring Dr. Antonio Noronha**
Adolescent binge drinking and stress induce adult AUD-like behaviors and changes in neurobiology
Chair: Fulton Crews

S38 Adolescent alcohol exposure produces alterations in pain processing in adulthood
Chandler Lawrence

S39 Emerging Roles of Non-Coding RNAs in Adult Psychopathology Following Early-Life Alcohol Exposure
Subash Pandey

S40 A Dorsolateral BNST-Parabrachial Nucleus Pathway Regulates Adolescent Alcohol-Induced Negative Affect in Females
Lucas Albrechet-Souza

S41 Proinflammatory HMGB1 and epigenetic contributions to persistent but reversible adolescent binge drinking- and stress-induced neuropathology
Ryan Peter Vetreno

4:30 p.m. – 5:30 p.m. **Poster Session and Snacks**

Thursday, May 14, 2026

8:00 a.m. - 9:00 a.m.

Plenary Lecture

PL2 Studying Alcohol Use Disorders and Stress with Genetically Selected Alcohol-Preferring msP Rats: Advantages, Challenges, and Future Directions
Roberto Ciccocioppo, Ph.D., Professor, University of Camerino, Italy

9:00 a.m. – 10:30 a.m.

Symposium X
Stress- and anxiety-sensitive brain circuits across species: Translational mechanisms of vulnerability for AUD
Chair: Marisa Silveri

S42 Distinct amygdala neuronal circuits regulating alcohol seeking and stress-induced drinking in mice
Junghyup Suh

S43 Salience-regulation circuit inefficiency as a pre-existing vulnerability in youth prior to substance use onset
Marisa Silveri

S44 A circuit-based strategy to delineate novel targets to ameliorate negative affective behavior during alcohol abstinence
Danny Winder

S45 Alterations in BNST connectivity during early abstinence in people with an alcohol use disorder
Jennifer Blackford

10:30 a.m. – 11:00 a.m.

Coffee Break

11:00 a.m. – 12:45 p.m.

Young Investigator Symposium
Chairs: Fulton Crews, Melissa Herman and Nikki Crowley

Y46 Blood RNA-based biomarkers for AUD
Laura Ferguson: 2026 Awardee

Y47 Binge alcohol consumption alters lateral habenula serotonin 5HT2c receptor signaling to enhance tonic firing and decrease bursting during abstinence
Meghan Flanigan: 2026 Awardee

Y48 Amygdala-cortical mechanisms linking social isolation to escalated alcohol consumption
Reesha Patel: 2026 Awardee

Y49 Muscarinic Acetylcholine Receptors in Alcohol Use Disorder
Leigh Walker: 2026 Awardee

Y50 Exploring the brain circuits of alcohol exposure induced negative affective states
Thomas Kash: 2011 Awardee

Y51 Brain circuits underlying control and compulsion
Andrew Holmes: 2008 Awardee

12:45 p.m. – 1:45 p.m.

Light Refreshments

1:45 p.m. – 3:15 p.m.

Symposium XI
New insights into the neural effects of alcohol across the lifespan, from molecules to circuits
Chairs: Jeff Weiner and Dorit Ron

S52 Striatal FGF2-FGFR1 upregulation and altered microRNA profiles in compulsive-like alcohol drinking
Segev Barak

S53 The ups and downs of BDNF signaling in the ventral hippocampus: Implications for the anxiolytic and anxiogenic actions of alcohol
Dorit Ron

S54 NR2F1 is a Cross-Species Mediator of Cerebral Cortex Defects Induced by Fetal Alcohol Intoxication
Sophie Laguesse

S55 Translational Insights into Alcohol Choice Behavior: The Role of BLA-vHPC Circuitry
Olivia Colarusso

1:45 p.m. – 3:15 p.m.

Symposium XII
Alcohol affects GABAergic fast-spiking interneurons throughout the forebrain
Chair: Max Joffe

S56 Perineuronal Net and Inhibitory Synapse Remodeling on Striatal Fast-spiking Interneurons by Alcohol
Brian Mathur

S57 Parvalbumin interneuron activation in prefrontal cortex reduces alcohol drinking in alcohol preferring rats
Kathleen Bryant

S58 Mechanisms Driving Binge Drinking: Alcohol-Induced Alterations in PFC Basket Cell Function and mGlu5 Receptor Signaling
Carly Fabian

Y59 Alcohol modulation of BLA network states involved in emotional processing
Jamie Maguire

3:15 p.m. – 4:45 p.m. **Symposium XIII**
Alcohol Effects: Recent developments on neuroimmune mechanisms and brain networks
Chairs: Marina Guizetti and Robert Messing
Discussant: Laura Ferguson

S60 Toll-like receptor 3 signaling in neurons regulates responses to ethanol through interferon and non-interferon dependent mechanisms
Robert Messing

S61 Sex-dependent reorganization of functional and structural brain networks in Alcohol Use Disorder: The Triple Network theory perspective
Pilar Ortiz Teba

S62 Glial cell diversity and molecular landscape of alcohol use disorder and animal models
Dayne Mayfield

S63 The Role of Microglia in Chronic Alcohol and Withdrawal
Sean Farris

4:45 p.m. – 5:45 p.m. **Poster Session and Snacks**

Friday, May 15, 2026

8:00 a.m. - 9:30 a.m. **Symposium XIV**
Alcohol and the Heart: Basic Science to Clinical Outcomes Affecting Stress, Craving and Excessive Alcohol Intake
Chairs: Rajita Sinha and David Eddie

S64 A Randomized Clinical Trial of Heart Rate Variability Biofeedback for Alcohol and Other Drugs Use Disorders
David Eddie

S65 Cardiac Interoception: A Window into Physiological Changes in Alcohol Use Disorder
Mateo Leganes-Fonteneau

S66 Integrated Cardio-behavioral Responses Define Emotional States
Jeremy Signoret-Genest

S67 Particular Anterior Insula outputs may mediate specific cardiac arousal regulation mechanisms during alcohol drinking and anxiety
Frederic Hopf

9:30 a.m. – 11:00 a.m. **Symposium XV**
Impact of Alcohol Exposure on Development of Emotional Regulation and Related Behaviors Across the Lifespan
Chairs: Jennifer Thomas and Rosana Camarini

S68 Evaluation of Early Prenatal Ethanol Exposure on Stress/Anxiety-Related Phenotypes
Kristin Hamre

S69 The impact of timing of developmental alcohol exposure on stress-associated neurobehavioral outcomes
David Linsenbardt

S70 Some depressing thoughts on how ethanol might affect synaptic communication
Brian Christie

S71 Insular Parvalbumin Interneurons as Modulators of Impulsivity and Ethanol-Seeking Behavior in Adolescent Mice
Fabio Cruz

11:00 a.m. – 11:30 a.m. **Coffee Break**

11:30 a.m. – 1:00 p.m. **Symposium XVI**
Role of Specific Amygdala and Cortical Cell Populations in Excessive Alcohol Drinking
Chair: Nicholas Gilpin

S72 Old dogs and new tricks in the search for treatments to reduce escalated alcohol drinking after stress
Nicholas Gilpin

S73 Single nucleus RNA sequencing identifies Fgf-R1 signaling in central amygdala as a neural substrate of punishment-resistant alcohol self-administration
Markus Heilig

S74 Sex differences of insular cortex function in persistent alcohol drinking in mice
Anna Beyeler

S75 Chronic Alcohol Reshapes Serotonin-Dynorphin Dynamics in the Nucleus Accumbens to Inhibit Social Reward
Catherine Marcinkiewcz

1:00 p.m. – 2:00 p.m. **Light Refreshments**

2:00 p.m. – 3:30 p.m. **Symposium XVII**
Alcohol and stress impacts on cortical limbic regulation of cognitive behavioral processes
Chair: Kathleen Grant
Discussant: Verginia Cuzon-Carlson

S76 Remembering to drink: Biases in forming alcohol-related episodic memories among risky drinkers
Elizabeth Goldfarb

S77 Impact of alcohol and stress on norepinephrine, frontal cortex dependent behaviors
Katy Nippert

S78 Sex-Dependent Neurophil Propagation Shapes Recurrent Dynamics in Primate Prefrontal Cortex
Suzanne Nolan

S79 Kappa Opioid Receptors on dopamine terminals drive anxiety-like behavior and hypodopaminergia in response to stress and alcohol exposure in mice
Katherine Holleran

2:00 p.m. – 3:30 p.m. **Symposium XVIII**
Individual differences in alcohol response and related outcomes: Behavioral and neurobiological mechanisms across species
Chair: Marcus Weera

S80 Neural epigenomic and transcriptomic landscape underlies individual variability in risk for AUD
Rita Cervera-Juanes

S81 Discrepancy-based resilience is associated with individual differences in problematic alcohol use and stress-related psychological and physical comorbidities
Melanie Schwandt

S82 Blunted lateral hypothalamus–lateral habenula circuit responses underlie reduced alcohol aversion in stress-susceptible 'Avoider' rats
Marcus Weera

S83 A neural circuit pathway for individuality in alcohol preference in Drosophila melanogaster
John Hernandez

3:30 p.m. – 5:00 p.m. **Symposium XIX**
Translational Studies on the Intersection of Alcohol Use Disorder and Chronic Pain
Chairs: Melanie Schwandt and Vijay Ramchandani

S84 Alcohol as an antecedent for chronic pain: prolongation of hypersensitivity after injury in a mouse model of consumption
Anna Lee

S85 Effects of Acute Alcohol Intake on Pain-related Brain Regions and Networks
Jeff Boissoneault

S86 Sex differences in chronic alcohol-induced mechanical allodynia: neuroimmune and endocannabinoid system dysregulation in the spinal cord and dorsal root ganglia of dependent mice
Vittoria Borgonetti

S87 Examining the moderating role of intolerance of uncertainty on pain tolerance and craving in patients with chronic pain and alcohol use disorder
Milena Radoman

6:30 p.m. – 10:00 p.m. **Closing Dinner**

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Alcoholism and Stress: A Framework for Future Treatment Strategies Volterra, Italy May 12 – 15, 2026

PLENARY LECTURES

PL1

Bringing back the light! Restoring hijacked alcohol motivation and adaptive stress responses from the dark side

Rajita Sinha, Ph.D.
Yale Stress Center, Yale University School of Medicine, New Haven, CT USA

Alcohol dramatically alters peripheral and central stress signaling networks and hijacks adaptive motivation to promote compulsive drinking. These chronic alcohol-related brain and body adaptations moves an individual to the "dark side" of health, with the development of alcohol use disorder (AUD) and increasing risk of a number of alcohol-related mental and physical illnesses. Drawing from human laboratory, brain imaging, physiological monitoring, longitudinal real world daily stress and drinking assessments and clinical treatment development research, Dr. Sinha will present the multiple whole-body effects of chronic alcohol intake, along with individual variations and heterogeneity in these effects, and their contribution to compulsive alcohol seeking and heavy alcohol intake. She will identify specific biobehavioral markers of continued alcohol intake and relapse risk, and discuss specific interventions that may reverse stress pathophysiology of AUD. Broad-based interventions targeting multi-system stress dysfunction to restore adaptive stress responses and motivation will be discussed. Results from specifically targeting catecholaminergic and neurosteroid pathways in randomized controlled trials will be presented to show effects on alcohol use, mood and related cardiac and liver risk outcomes. Early work on restoring adaptive stress responses and motivation with brief behavioral stress interventions to reduce risk of AUD and AUD relapse will also be presented. Together, these findings will facilitate discussions on challenges in tackling heterogeneity of chronic alcohol effects and precision medicine approaches and novel strategies for AUD prevention, treatment and recovery.

https://doi.org/10.1016/j.alcohol.2026.01.003

PL2

Studying Alcohol Use Disorders and Stress with Genetically Selected Alcohol-Preferring msP Rats: Advantages, Challenges, and Future Directions

Roberto Ciccocioppo, Ph.D.
International School of Advanced Studies, University of Camerino, Italy

Genetically selected alcohol-preferring Marchigian Sardinian (msP) rats have been bred for over 100 generations at the University of Camerino (Italy), starting from the progenitor Sardinian alcohol-preferring (sP) line originally established at the University of Cagliari. This strain is characterized by a strong innate propensity for excessive alcohol consumption, accompanied by pronounced anxiety- e and depressive-like traits. A key genetic alteration identified in msP rats is a mutation in the gene encoding corticotropin-releasing factor receptor 1 (*Crhr1*), which results in a widespread overactivity of the CRF1R system compared to the Wistar background strain.

Importantly, beyond CRF1R overexpression, msP rats exhibit a broad dysregulation of multiple genes associated with stress-related mechanisms. Among these, a generalized upregulation of genes encoding opioid peptides (e.g., dynorphins, nociceptin) and opioid receptors (MOP, NOP, KOP) has been observed. Recent studies further show that, despite being selectively bred for high alcohol preference, msP rats display an enhanced innate susceptibility to self-administer other drugs of abuse, including cocaine and heroin. Notably, a viral, selective knockdown of the MOP receptor in the ventral tegmental area markedly reduced the elevated heroin intake observed in msP rats. These findings suggest the presence of heritable traits that confer vulnerability to substance use disorders independently of the specific drug. Moreover, they support the view that msP rats constitute a valuable model for studying polysubstance abuse. Ongoing investigations aim to evaluate the translational relevance of this rat line for the identification of novel molecular targets to treat not only alcohol dependence but also other forms of drug addiction.

https://doi.org/10.1016/j.alcohol.2026.01.004

ROUNDTABLE

R29

Clinical Trial Roundtable

Chairs: Katie Witkiewitz, Ph.D., Professor [1], Carolina Haass-Koffler, Ph.D., Associate Professor [2]
[1] *University of New Mexico, Albuquerque, NM, USA;* [2] *Brown University, Providence, RI, USA*

This roundtable will highlight cutting-edge clinical trials targeting alcohol use disorder (AUD) in the context of stress-related psychopathology, a highly prevalent and clinically challenging comorbidity that contributes to poorer outcomes, greater relapse risk, and limited treatment response. AUD rarely occurs in isolation; chronic stress exposure and stress-related disorders such as posttraumatic stress disorder (PTSD) and alcohol-associated liver disease (ALD) profoundly shape disease trajectory, treatment engagement, and recovery. This session will emphasize how emerging mechanistic insights are informing innovative trial designs and novel therapeutic strategies for this complex patient population. Drs. **Katie Witkiewitz** and **Carolina Haass-Koffler** will moderate a multidisciplinary discussion among six speakers with complementary expertise in clinical trials spanning pharmacologic, behavioral, and psychedelic-assisted interventions. Dr. **Mack Mitchell** will address the role of stress, craving, and stigma in individuals with AUD and ALD, with a focus on how these factors intersect with novel pharmacological targets, including glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and fibroblast growth factor-21 (FGF-21) analogues. Dr. **Patrick Bach** will present findings on the interaction between psychosocial stress, alcohol cue reactivity, and craving in driving alcohol consumption and relapse, as well as the therapeutic potential of cannabidiol. Drs. **Christy Capone** and **Erica Eaton** will present emerging data from an MDMA-assisted therapy (MDMA-AT) program for Veterans with comorbid PTSD and AUD, including findings from an open-label pilot study and an ongoing randomized, placebo-controlled clinical trial. Dr. **Roberta Agabio** will synthesize evidence from systematic reviews and meta-analyses examining AUD and stress-related disorders, with particular attention to dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, cortisol and relationship with alcohol use. Dr. **Anne Fernandez** will discuss novel methodologies for identifying and engaging patients with undiagnosed AUD during routine medical care, and also present data on the need to provide tailored interventions for the stress-AUD intersection among individuals with severe medical illnesses and ongoing alcohol use. Finally, Dr. **Markus Heilig** will provide insights from genetically informative approaches—including twin studies, family-based designs, and Mendelian randomization—to disentangle gene–environment interactions underlying stress vulnerability and AUD risk, with implications for precision medicine and individualized treatment development. Importantly, this session will also be highly relevant to basic scientists working with preclinical models of AUD and stress-related disorders. By highlighting clinical trial outcomes, patient

heterogeneity, and mechanistic targets emerging from human studies, the roundtable will provide critical insights that can inform the refinement of preclinical models to better capture the complexity of AUD–stress comorbidity. Aligning animal models with clinically meaningful phenotypes, such as stress-induced drinking, relapse vulnerability, neuroendocrine dysregulation, and trauma-related symptom clusters, will strengthen translational validity and accelerate the development of treatments for this notoriously difficult-to-treat population. Together, this roundtable with investigators from different background, nationality and career stage will underscore the importance of addressing AUD–stress comorbidity in clinical trials and will highlight innovative, mechanism-driven approaches and novel methodologies that have the potential to transform treatment outcomes for individuals with AUD.

https://doi.org/10.1016/j.alcohol.2026.01.005

Presenters:
Alcohol Use in Clinical Trials for Treatment of Alcohol-associated Liver Disease

Mack Mitchell, M.D., Professor of Internal Medicine
Univ. of Texas Southwestern Medical Center, Dallas, TX, USA

Alcohol-associated liver disease (ALD) accounts for 50% of deaths from liver disease worldwide. Previous studies on treatment of ALD have focused primarily on the complications of liver disease rather than the cause. Numerous studies have examined treatment of severe alcohol-associated hepatitis (sAH), a devastating complication of ALD with mortality up to 25% within 90 days or on the complications of decompensated ALD such as encephalopathy, variceal hemorrhage and ascites, but few have examined treatments that prevent progression of fibrosis and decompensation or promote "regression/recompensation." Most studies indicate that 75-80%, but not all patients with ALD have an underlying alcohol use disorder (AUD). Other studies indicate that continued consumption of alcohol after a diagnosis of ALD is associated with progression of fibrosis, the major determinant of major adverse liver outcomes (MALO). Newer noninvasive methods for assessing fibrosis including biomarkers in blood, liver stiffness assessed by elastography (Fibroscan or magnetic resonance elastography) will soon replace liver biopsy as a surrogate for MALO. New guidance from FDA indicates a willingness of the agency to consider these surrogates in metabolic associated steatotic liver disease (MASLD) which will pave the way for similar biomarkers in ALD.
Increasing recognition of the role of continued alcohol consumption in progression of ALD is leading to a search for better ways to reduce alcohol consumption in this population. Consensus is emerging to integrate pharmacotherapy and intensive behavioral therapy for AUD into research protocols and treatment algorithms. Newer drugs including GLP-1 agonists and possibly FGF-21 analogues have the potential to treat both steatotic liver disease and AUD. The roles of stress, craving and stigma have not been examined carefully in patients with ALD. Designing research studies to incorporate assessment and treatment of both ALD and AUD is essential to improving both liver and alcohol use outcomes for this population of people with end organ damage from excessive alcohol consumption.

https://doi.org/10.1016/j.alcohol.2026.01.006

Novel evidence on the interaction of psychosocial stress and craving in alcohol use disorder and the potential of targeted interventions with cannabidiol

Patrick Bach, M.D., Ph.D., Professor
Central Institute of Mental Health, Mannheim, Germany

Alcohol use disorder (AUD) is characterized by complex interactions between psychosocial stress, alcohol cue reactivity, and craving that drive alcohol consumption and relapse. This talk presents novel findings from four studies investigating these mechanisms and the therapeutic potential of cannabidiol (CBD). First, evidence from a randomized controlled neuroimaging study demonstrates that psychosocial stress induces sensitization of alcohol cue-related activation in the left anterior insula, which is predicted by cortisol levels and associated with alcohol craving and prospective alcohol use during 12-month follow-up. Second, data from a longitudinal cohort study reveals that individual stress reactivity predicts alcohol craving in both experimental and real-life settings. Third, findings from the double-blind randomized ICONIC trial show that acute administration of 800 mg CBD significantly reduced cue-induced nucleus accumbens activation and alcohol craving following combined stress and cue exposure in individuals with AUD, with effects showing significant plasma level-response associations. Fourth, CBD attenuated bilateral amygdala reactivity to negative emotional stimuli, with amygdala response correlating positively with subjective craving and negatively with CBD plasma levels. Together, these findings advance understanding of stress-craving interactions in AUD and support CBD's potential as a targeted intervention addressing both cue-induced and negative affect-driven craving mechanisms.

https://doi.org/10.1016/j.alcohol.2026.01.007

MDMA-Assisted Therapy for Veterans with PTSD and Alcohol Use Disorders: Considerations for Randomized Controlled Trials

Christy Capone, Ph.D., Erica Eaton, Ph.D., Assistant Professors
Brown University, Providence, RI, USA

Posttraumatic stress disorder and co-occurring alcohol use disorder (PTSD–AUD) create reinforcing cycles of avoidance, hyperarousal, and alcohol-mediated negative reinforcement that sustain symptoms and hinder treatment. Within the Veterans Health Administration, an estimated 63% of Veterans with a substance use disorder also have PTSD, and those with PTSD–AUD present with greater symptom severity, higher suicide risk, and poorer treatment response than individuals with either disorder alone.
Treatment options remain limited. Pharmacotherapies for AUD show modest and inconsistent effects in those with comorbid PTSD, and although gold-standard trauma-focused psychotherapies such as PE and CPT are effective for many, a substantial proportion of patients retain clinically significant symptoms. Engagement and retention challenges—particularly among Veterans with co-occurring substance use—underscore the need for more effective approaches.
This clinical roundtable presents emerging findings from our MDMA-assisted therapy (MDMA-AT) program for Veterans with PTSD–AUD, including results from an open-label pilot and an ongoing randomized, placebo-controlled trial. Pilot data demonstrate strong retention, high acceptability, and a favorable safety profile, supporting the feasibility of MDMA-AT in Veteran settings. We will also describe the design of the first placebo-controlled randomized clinical trial of MDMA-AT in this population ($N = 80$), consisting of three once-monthly Experimental Sessions with divided-dose MDMA-HCl and accompanying preparatory and integrative therapy.
Together, these studies highlight the promise of MDMA-AT to address the complex, mutually reinforcing processes underlying PTSD–AUD in Veterans.

https://doi.org/10.1016/j.alcohol.2026.01.008

Hidden in Plain Sight: Identifying and Treating Alcohol Use Disorder in Medical and Surgical Populations

Anne Fernandez, Ph.D., Associate Professor
University of Michigan Medical School, Ann Arbor, MI, USA

Medical and surgical patients with alcohol use disorder (AUD) face compounded health risks yet remain systematically underrepresented in alcohol-related clinical research. This presentation examines innovative approaches for identifying and treating AUD and unhealthy alcohol use in these overlooked populations, emphasizing how medical crises and routine medical procedures create critical intervention opportunities. Dr. Fernandez will present novel methodologies including natural language processing algorithms to identify patients with undiagnosed AUD during routine medical care. She will demonstrate how acute medical concerns serve as powerful motivational leverage points for engaging patients in alcohol treatment and intervention. She will present the urgent need for tailored behavioral and pharmacotherapeutic approaches at the intersection of medical illness and alcohol use. Special focus will be given to populations undergoing surgery or receiving life-changing diagnoses, where alcohol-related complications pose heightened perioperative and disease management risks, while simultaneously limiting the use of current alcohol pharmacotherapies. By bridging addiction care and other medical specialties, the field has an opportunity to expand treatment access to vulnerable populations routinely excluded from AUD clinical trials, helping to close a critical care gap.

https://doi.org/10.1016/j.alcohol.2026.01.009

Alcohol Use Disorder and Stress: Systematic Reviews and Meta-Analyses on the Topic

Roberta Agabio, M.D.
Department of Biomedical Sciences, University of Cagliari, Italy

A complex relationship exists between alcohol consumption and stress. According to the self-medication hypothesis, alcohol can be consumed to reduce negative feelings of stress or anxiety symptoms and increase sedation. Alcohol consumption, in turn, alters indicators used to assess stress, such as levels of cortisol, the main steroid hormone synthesized by the hypothalamic-pituitary-adrenal (HPA) axis. Cortisol levels are used to study the relationship between stress and alcohol consumption. The relationship between alcohol use and stress is complicated by the fact that both stress and alcohol consumption can occur in both acute and chronic forms, and in individuals with or without mental disorders such as post-traumatic stress disorder and/or alcohol use disorder (AUD). My presentation aims to summarize the information available in the literature on stress and alcohol use among people with AUD. To achieve this goal, a literature search will be conducted to identify systematic reviews and meta-analyses that have investigated the relationship between alcohol consumption and stress in people with AUD and summarize the findings of the studies identified.

https://doi.org/10.1016/j.alcohol.2026.01.010

Re-examining the role of environmental risk factors in alcohol use disorder

Markus Heilig, M.D., Ph.D., Professor of Psychiatry
Linkoping University, Sweden

Genetic factors account for approximately 50% of variance in AUD risk, but for the foreseeable future, only environmental factors remain modifiable. Understanding the role of environmental risk may also offer opportunities for personalized approaches to treatment. However, disentangling the role of environmental and genetic risk is challenging. Because of gene – environment correlations (rGE; passive, evocative or active), environmental exposures are not randomly distributed. As a result, statistical associations in epidemiological data cannot easily be interpreted in causal terms. Genetically informative studies that use twin, familial or Mendelian Randomization approaches offer opportunities for disentangling this complex web of causality. Here, insights from studies that have used these approaches will be presented, as applied to three environmental risk factors that have received extensive attention in AUD research: early onset of alcohol use, early life adversity, and low socioeconomic status. In all three cases, there will be surprises, with potential implications for policy as well as treatment. These will be discussed.

https://doi.org/10.1016/j.alcohol.2026.01.011

YOUNG INVESTIGATORS
Young Investigators Symposium
Chairs: Fulton T. Crews, Melissa Herman and Nikki Crowley
Y46
Blood RNA-based biomarkers for AUD

L.B. Ferguson, V.A. Ramchandani, N. Diazgranados, R.O. Messing

Background: Transcriptomic profiling of accessible tissues such as whole blood offers a promising avenue for precision medicine approaches in psychiatric and substance use disorders, where direct access to brain tissue is limited. Prior work from animal models demonstrates that blood RNA profiles can accurately classify ethanol exposure status using machine learning, suggesting potential translational utility for human alcohol use disorder (AUD).
Objective: This study tests the hypothesis that there is a transcriptional signature of AUD in blood that persists into withdrawal and can discriminate between individuals with AUD and matched controls.
Methods: Whole blood RNA sequencing was performed from 50 non-AUD control participants and 50 AUD patients sampled at multiple timepoints during inpatient withdrawal and early recovery. Rigorous quality control, normalization, and covariate adjustment were applied before model training. Machine learning classifiers including elastic net logistic regression and additional algorithms (random forest, XGBoost, and partial least squares discriminant analysis), were trained to distinguish AUD from control samples. To enhance robustness, models are being evaluated across multiple analytical conditions, with stable RNA features identified by their recurrence across models and validation using independent longitudinal blood transcriptome datasets.
Results and ongoing analyses: Preliminary models trained on blood RNA profiles demonstrate strong potential for discriminating AUD and control samples. A subset of RNAs consistently contribute to classification across modeling conditions and exhibit longitudinal stability, making them promising candidates for biomarker development. Ongoing analyses are focused on identifying the most robust RNA and algorithmic combinations to support replication and clinical translation.
Conclusions: These findings support the feasibility of developing blood RNA-based biomarkers for AUD and highlight the importance of methodological robustness in advancing transcriptomic signatures toward clinical application.

https://doi.org/10.1016/j.alcohol.2026.01.012

Y47
Binge alcohol consumption alters lateral habenula serotonin 5HT2c receptor signaling to enhance tonic firing and decrease bursting during abstinence

S. Choi, G. Dodis, M. Flanigan

Previous work has demonstrated that chemogenetic inhibition of lateral habenula (LHb) 5HT2c receptor-containing neurons (5HT2c+) reduces affective symptoms of alcohol withdrawal in mice of both sexes. However, whether serotonin signaling through 5HT2c receptors is modified during abstinence has not been determined. First, we subjected male and female mice to 3 weeks of drinking in the dark (DiD) followed by one week of abstinence and performed patch clamp electrophysiology in LHb 5HT2c+. This revealed that DiD produces long-lasting adaptations in 5HT2c receptor signaling whereby responses to serotonin are dampened but constitutive signaling is enhanced. Specifically, enhanced tonic firing in DiD mice was normalized by 5HT2c antagonism in a serotonin-independent manner. Further, DiD dampened bursting while also occluding the suppressive effect of serotonin on bursting, and antagonism of 5HT2c increased bursting in DiD mice in a similarly serotonin-independent manner. Given that 5HT2c expresses up to 24 distinct isoforms with different levels of constitutive activity and serotonin sensitivity, we next performed targeted amplicon sequencing of the Htr2c transcript edited region to evaluate if DiD was producing these physiological effects through altered isoform expression. While this analysis is currently in progress, we hypothesize that DiD increases the expression of the unedited (INI) 5HT2c isoform, resulting in increased 5HT2c constitutive activity. In line with this hypothesis, we found that DiD downregulates the RNA-editing enzyme ADAR1b, potentially suggesting it is mediating the changes in LHb 5HT2c isoform balance after alcohol exposure to alter physiology and behavior during withdrawal.

https://doi.org/10.1016/j.alcohol.2026.01.013

Y48
Amygdala-cortical mechanisms linking social isolation to escalated alcohol consumption

Ana Waltrick, Xianru Yu, Dahee Jung, Hao Li, Reesha R. Patel

Social isolation is a major public health concern and a risk factor for alcohol misuse, with opposite effects in men and women. Loneliness predicts increased drinking in men but reduced drinking in women. We found that adult social isolation escalated voluntary alcohol intake in male mice but decreased intake in females. These divergent behaviors were mirrored by basolateral amygdala (BLA)-medial prefrontal cortex (mPFC) circuit function, where isolation increased BLA-mPFC excitability in males but reduced it in females, with females showing higher baseline excitability that tracks with higher alcohol intake. This suggests that BLA-mPFC is a shared neural substrate that is differentially adapted during social isolation. To uncover downstream targets driving drinking, we focused on mPFC corticotropin-releasing factor (CRF) and its type-1 receptor-expressing (CRFR1+) neurons, which receive direct BLA input. In males, isolation increased activation and intrinsic excitability of CRF-expressing (CRF+) neurons and enhanced BLA-mediated glutamate release onto them. Fiber photometry revealed robust isolation-induced alcohol-evoked CRF release in the mPFC in males, absent in females. This suggests that social isolation sensitizes mPFC CRF+ neurons and CRF release to alcohol, pointing to a potential neuromodulatory mechanism linking CRF signaling to escalated

drinking. Neighboring CRFR1 + pyramidal neurons showed heightened alcohol-evoked calcium activity during isolation, and optogenetic activation of these neurons increased alcohol intake. These findings support a model in which isolation biases BLA-mPFC computations toward alcohol use via mPFC CRF driven neuromodulation and CRFR1 + neurons. This work identifies a sex-divergent, cell type-resolved circuit mechanism that links social isolation to vulnerability for alcohol misuse.

https://doi.org/10.1016/j.alcohol.2026.01.014

Y49
Muscarinic Acetylcholine Receptors In Alcohol Use Disorder

Leigh C. Walker, Roberta Anversa, Alice E. Berizzi, Nicola A. Chen, Patricia Rueda, Victoria M. Perreau, Kade Huckstep, Craig W. Lindsley, Carrie K. Jones, Darren M. Riddy, Arthur Christopoulos, Christopher J. Langmead, Howard C. Becker, Andrew J. Lawrence

Despite the large socioeconomic burden of alcohol use disorders (AUD), therapeutic treatment options remain limited. There is a need to characterise the neurochemistry underpinning alcohol seeking to aid identifying and evaluating novel targets. Muscarinic acetylcholine receptors (mAChRs) are potential targets for AUD treatment as they are expressed within the mesocorticolimbic reward system, including dense expression in the striatum, amygdala and ventral hippocampus. Here they indirectly act to modulate dopamine release, which may regulate reward processing. Our data highlight the differential roles of M1, M4 and M5 subtype mAChRs in alcohol consumption, motivation and seeking. We use Genome wide RNA sequencing and qPCR to identify regions which have dysregulation of mAChRs following chronic alcohol consumption, and selective allosteric modulators to directly assess their roles in alcohol consumption and seeking. Our data highlight a translationally relevant rodent model of alcohol consumption that recapitulates dysregulation observed in individuals with AUD, and expand our understanding of key brain regions that are involved in driving different aspects of this behaviour.

https://doi.org/10.1016/j.alcohol.2026.01.015

Y50
Exploring the brain circuits of alcohol exposure induced negative affective states

Thomas Kash
UNC Chapell Hill School of Medicine

Heightened negative affective state during alcohol abstinence is a hallmark feature of, and major contributor to, Alcohol Use Disorder (AUD). However, the neural circuit mechanisms that drive this heightened negative affective state are not well understood. Work from many labs have identified the extended amygdala as a potential key site of negative affective states. Current work in the lab focuses on understanding how alcohol exposure can drive changes in signaling and dynamics in the extended amygdala, and how that drives aberrant behavior. This presentation will explore these relationships using in vivo fiber photometry, slice physiology and machine learning based analysis of behavior.

https://doi.org/10.1016/j.alcohol.2026.01.016

Y51
Brain circuits underlying control and compulsion

Andrew Holmes

Understanding the mechanisms that drive excessive alcohol use remains a critical challenge in addiction neuroscience. Our work focuses on developing novel models of compulsive alcohol and reward seeking that more accurately capture the transition from controlled to pathological intake. Using these models, we aim to elucidate the neural circuit and neuromodulator mechanisms underlying alcohol and reward seeking, with an emphasis on how disruptions in signaling across interconnected brain regions promote maladaptive behavior. Complementary structural and functional analyses build upon studies showing the deleterious effects on the structure and function of key cortical, limbic, and striatal regions, including deficits in prefrontal regulation, heightened responsivity of limbic circuits, and altered striatal plasticity. By integrating behavioral assays with circuit-level and molecular approaches, the proposed work seeks to identify the causal pathways through which chronic alcohol exposure reshapes neural computation to bias decision-making toward compulsive reward pursuit. Ultimately, this research aims to advance mechanistic models of addiction and reveal potential targets for intervention that restore adaptive control over reward-seeking behaviors.

https://doi.org/10.1016/j.alcohol.2026.01.017

SYMPOSIA
Symposium I
The Interface of Stress, Alcohol and Endocannabinoids: A Memorial Session for Larry Parsons
Dedicated to the Memory of Loren H. Parsons, Ph.D.
Chair: Matthew Hill
S3
Stress Differentially Regulates Discrete Projection Populations from the Basolateral Amygdala

Matthew Hill

The basolateral amygdala (BLA) is reliably activated by psychological stress in both humans and rodents and influences diverse behavioral and physiological processes involved in stress adaptation. The BLA also represents the primary brain region through which cannabinoids exert their effects on stress and emotional states. The functional organization of distinct BLA circuits and their contribution to stress-induced activation of the neuroendocrine response is unclear. The current data demonstrate that: (i) BLA projection neurons are necessary and sufficient for stress-induced neuroendocrine activation; (ii) projection populations have a heterogeneous spatial distribution across the BLA; (iii) diverse BLA populations targeting the prelimbic cortex, nucleus accumbens, bed nucleus of stria terminalis, central amygdala, lateral hypothalamus, and ventral hippocampus are activated by acute stress, with the location of activated populations biased toward the medial basal amygdala; and (iv) inhibition of singular projections does not recapitulate global inhibition of BLA projection neurons. Using patch clamp electrophysiology, we are further examining projection-specifc changes induced by stress and how cannabinoid receptor signaling influences the activation of these discrete projections.

https://doi.org/10.1016/j.alcohol.2026.01.018

S4
Interactions between acute alcohol consumption and peripheral endocannabinoids on brain and behavioral correlates of reward and threat responding in humans

Leah Mayo

The endocannabinoid system is a key mediator of stress processing and is also believed to contribute to the reward-related effects of several recreationally used drugs, including alcohol. Individuals with a history of alcohol use disorder demonstrate dysregulation of the endocannabinoid system. However, less is known about the acute effects of alcohol on the endocannabinoid system and how this may relate to the impact of alcohol on reward or threat processing in humans.

Here, healthy adults (N=32) completed a within-subjects, placebo-controlled study in which they were administered alcohol (0.6 g/kg) or placebo on separate occasions. In both sessions, participants completed fMRI scans consisting of tasks measuring threat and reward processing. Blood samples were collected throughout both sessions for analysis of endocannabinoid levels.

Results indicate that acute alcohol administration resulted in reduced 2-AG levels, with greater alcohol-induced decreases in 2-AG associated with more positive subjective alcohol effects. In contrast, AEA levels were correlated to the magnitude of neural responses to reward cues; a relationship that was unaffected by alcohol administration. Ongoing analyses are exploring the association between alcohol and endocannabinoids during threat reactivity.

In sum, we found divergent effects of AEA and 2-AG in relation to the neural correlates of reward processing and subjective response to alcohol, respectively. These findings highlight potential neurobiological mechanisms contributing to the individual variability ni response to alcohol, and perhaps vulnerability to problematic use.

https://doi.org/10.1016/j.alcohol.2026.01.019

S5

Cannabinoid Modulation of Central Amygdala Population Dynamics During Threat Investigation

Farhana Yasmin, Saptarnab Naskar, Luis E. Rosas-Vidal, Sachin Patel

Cannabinoids can enhance stress responses and threat reactivity in humans and rodents; however, the mechanisms by which cannabinoids modulate neural representation of threat-related stimuli and defensive behavior are not known. We will present data that cannabinoid administration augments defensive responses to predator odor threat and increases the activity of central amygdala (CeA) somatostatin neurons (SOM) and alters basal network dynamics in a manner supporting generation of antagonistic sub-ensembles within the SOM population at high doses. Moreover, diverging neuronal population trajectory dynamics and enhanced antagonistic sub-ensemble representation of threat-related behaviors, and enhanced threat-related location representation, were also observed. Lastly, cannabinoid administration increased the proportion of SOM neurons exhibiting multidimensional representation of threat-related behaviors and behavior-location conjunction. While cannabinoid receptor activation ex vivo suppressed long-range excitatory inputs to SOM neurons, our data suggest preferential suppression of local disynaptic GABA release subserves cannabinoid activation of CeA SOM neurons. These data provide insight into how cannabinoid-mediated presynaptic suppression transforms postsynaptic population dynamics and reveal cellular mechanisms by which cannabinoids augment threat-reactivity, while revealing cellular mechanisms underlying common adverse effects of cannabis use.

https://doi.org/10.1016/j.alcohol.2026.01.020

S6

Endocannabinoid mediated frontal cortical control in adaptive stress coping and subsequent alcohol drinking

Laura C. Ornelas

Alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD) are highly comorbid, which may be driven by inadequate cortical control over maladaptive stress responses that lead to increases in alcohol drinking.
Work presented will examine the role of endocannabinoid signaling with the mPFC in modulating maladaptive stress coping behavior and subsequent alcohol drinking. We have previously shown that female rats that engaged in greater active coping behaviors (digging) during exposure to the synthetically produced predator odor trimethylthiazoline (TMT) showed increases in alcohol self-administration. In contrast, males and females that engaged in greater passive coping behavior (immobility) during the TMT exposure showed decreased or no increases in alcohol drinking. In addition, we show that TMT exposure produces increases in arachidonic acid (enzymatic degradation product of 2-eCBs) in the prelimbic (PrL) cortex in rats that engage in active coping behavior during TMT, suggesting greater degradation of eCB levels in the PrL is key to regulating stress responsivity. Dr. Ornelas will also discuss the role of the endocannabinoid system in modulating E/I imbalance within the mPFC to promote adaptive responses to stress. We show that rats that engaged in greater maladaptive coping behavior during TMT showed a trend for increased GABA levels in the PrL and reduced GAT1 expression. Considering GAT1 mediates the reuptake of GABA, lack of GAT1 expression could lead to more extracellular GABA and increased tonic inhibition.
Determining the molecular and cellular mechanisms underlying maladaptive stress coping and alcohol drinking may provide more effective treatment strategies for individuals with PTSD and AUD.

https://doi.org/10.1016/j.alcohol.2026.01.021

Symposium II
Converging mechanisms of pain, anhedonia and alcohol use disorders
Chair: Lucia Hipolito

S7

Crosstalk of the opioid receptors and neuroinflammation: role in pain, anhedonia and alcohol intake in rats.

Lucia Hipolito

The endogenous opioidergic system critically regulates the mesocorticolimbic system (MCLS), aversion and reinforcement, including alcohol reinforcement. Pharmacological blockade of mu- and kappa-opioid receptors (MOR, KOR) reduces alcohol reinforcement and abstinence-induced negative affect, respectively. In parallel, alcohol triggers neuroinflammatory responses and negative affective states that can persist during abstinence and promote relapse. Chronic inflammatory pain further increases relapse vulnerability in female rats. In our model, relapse-like behavior was accompanied by anxiety-like behavior, MOR/KOR alterations, and microglial activation in the MCLS. Strikingly, the temporal dynamics of MOR changes paralleled those of microglial activation, suggesting a functional MOR–neuroimmune crosstalk in pain-induced alcohol relapse-like behavior. Here, we combined behavioral assays, in vivo microdialysis, immunohistochemistry, cell culture, and biochemical approaches to investigate this crosstalk between opioid receptors and the neuroimmune responses in the MCLS. Our data reveal MOR–neuroinflammation crosstalk, with no significant involvement of KOR. MOR activation in the nucleus accumbens (NAc) and ventral tegmental area induced neuroinflammatory responses and pain altered these effects. Conversely, activated microglia and proinflammatory cytokines enhanced MOR signaling and expression in vitro, as well as induced altered motivated behavior in vivo, correlating with pain-induced loss of motivation.
These findings provide in vivo and in vitro evidence of bidirectional MOR–microglia crosstalk. Given the established roles of MOR signaling, neuroinflammation, and negative affect in alcohol use disorder, this mechanism may underlie the heightened relapse vulnerability observed under inflammatory pain. Elucidating this crosstalk could help identify novel therapeutic targets for AUD.

https://doi.org/10.1016/j.alcohol.2026.01.022

S8

Non-synaptic basis of addiction: translational MRI evidence in alcohol use disorders

Santiago Canals

Alcohol use disorder (AUD) induces profound microstructural alterations in both gray and white matter that contribute to cognitive and functional impairments. In this presentation, I will review recent work from our laboratory employing translational diffusion-weighted MRI approaches in both humans and rodent models to elucidate the neurobiological mechanisms underlying these changes. Our findings reveal that increased mean diffusivity (MD) in gray matter reflects microglial activation and reduced extracellular space tortuosity, which together may facilitate aberrant volume neurotransmission. In parallel, decreases in fractional anisotropy (FA) within white matter indicate progressive disruption of major fiber tracts, particularly the fimbria/fornix, a pathway critically involved in cognitive flexibility and memory processes. Longitudinal analyses further demonstrate that these white matter alterations not only persist but may even accelerate during the early stages of abstinence. Importantly, we will discuss how such non-synaptic cellular and glial changes may reshape large-scale brain dynamics and functional connectivity. Finally, I will explore emerging therapeutic avenues that may foster structural recovery by enhancing myelin and glial plasticity. Together, these findings provide new insights into the pathophysiological continuum of AUD and identify potential targets for intervention aimed at improving brain health and clinical outcomes during recovery.

https://doi.org/10.1016/j.alcohol.2026.01.023

S9

CeA-vlPAG Circuit Regulation of Adolescent Alcohol-induced Hyperalgesia

Tiffany Wills

Adolescence is when alcohol use is initiated, and it's early use is the highest predictor for the development of alcohol use disorders. In recent years, we have begun to explore the long-term effects of AIE on pain. In adults, it is known that acute alcohol can alleviate pain, while chronic alcohol use and withdrawal produces hyperalgesia or worsens pre-existing pain states. Our work finds that AIE produces long-term mechanical and thermal hyperalgesia in male and female Wistar rats and C57BL/6J mice. This hyperalgesia rodents. AIE also enhances pain-like responses to a formalin pain challenge in adulthood. The central amygdala (CeA) is a known hub for the regulation of pain. The CeA sends GABAergic projections to the ventral periaqueductal gray (vlPAG), a region critical for descending modulation of pain. Our work finds that a history of AIE decreases the synaptic drive in vlPAG-projecting CeA cells and blunts the c-Fos

response in these cells to a formalin challenge.
Chemogenetically enhancing PAG-projecting CeA cells reduces AIE-induced hyperalgesia. The vlPAG contains a transcriptionally diverse population of excitatory and inhibitory neurons that are involved in both enhancing and inhibiting pain. Bulk RNAseq of vlPAG finds numerous genes regulated by AIE, several of which have been implicated in other pain conditions. Recordings of vlPAG cells find an AIE-induced increase in excitatory drive within certain cells. Future work will further explore the CeA-vlPAG circuit and specific cell types involved in AIE-induced hyperalgesia. These long-term changes in nociception could drive future alcohol use and/or increased sensitivity to pain.

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S10
Role of a dynorphinergic CeA to BNST input in pain-induced anhedonia

Jose Moron

Pain consists of two critical factors: a *sensory* component important for localizing and discriminating pain intensity and an *affective* component contributing to emotional, motivational, and aversive responses to noxious stimuli. The inextricable nature of these two processes contributes to the co-occurrence of pain and mood disorders - comorbidities additively influencing pain intensity and chronicity, pain-related disability, and reduced treatment efficacy. Therefore, comprehensive and effective treatment of pain pathophysiology rests on our ability to target systems controlling both sensory *and* affective components of pain. The dynorphin (Dyn)-kappa opioid receptor (KOR) system is activated in response to pain and regulates tonic-aversive states produced by pain, including allodynia, increased anxiety- and depressive-like behaviors, and disrupted motivational states. However, the precise means by which Dyn-KOR function simultaneously regulates both dimensions of pain (i.e. sensory and affective) remain unclear. In this talk we will present new data supporting the expression of a population of prodynorphin-containing neurons in the central amygdala projecting to the bed nucleus of the stria terminalis (CeA^{pDyn}→BNST) capable of encoding *both* pronociception *and* pain-induced negative affect. To this end, we found that inflammatory pain reduces inhibitory drive from CeA^{pDyn} neurons *ex vivo*. Similarly, chemogenetic inhibition CeA^{pDyn}→BNST activity *in vivo* can produce hyperalgesia in the absence of pain; while excitation of CeA^{pDyn}→BNST activity is analgesic. We also found that CeA^{pDyn}→BNST activity encodes *affective pain*, often revealed behavioral mood disruption, pain avoidance, and anhedonia. Altogether, this suggest that stress-associated activation of the CeA^{pdyn}→BNST pathway is an important feedback mechanism in reducing the suppressive effects of pain underlying nociceptive and affective pain aversion.

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Symposium III
Caught in the Middle: Midline Thalamic Mechanisms of Vulnerability to Stress and Alcohol
Chairs: Kristen Pleil and Jennifer Rinker
Discussant: David Lovinger
S11
Alcohol dependence disrupts stress-sensitive thalamic inputs onto accumbal parvalbumin interneurons to promote alcohol seeking

Jennifer A. Rinker, Amy L. Ward, Kion T. Winston, Lisa M. Green, Cynara J. Cooper, Sophie Bumaier, Rachel E. Clarke, Jacqueline E. Paniccia, Elizabeth M. Doncheck, Roger I. Grant, Kelsey M. Vollmer, James M. Otis

Nucleus accumbens (NAc) parvalbumin interneurons (PV-INs) receive robust innervation from the paraventricular thalamus (PVT), a midline thalamic nucleus known for its role in suppressing reward seeking in response to stressors. Given that a hallmark of alcohol dependence is a loss of inhibitory control over alcohol seeking, we hypothesized that alcohol dysregulates the PVT-$NAc^{PV\text{-}IN}$ circuit, promoting alcohol seeking. To investigate this, we examined the effects of alcohol dependence on single-cell activity of both PVT inputs to the NAc and $NAc^{PV\text{-}INs}$ using 2-photon calcium-imaging.
Preliminary analyses show reduced calcium dynamics in both PVT-NAc neurons and $NAc^{PV\text{-}IN}$ during alcohol seeking. Further, we show that alcohol dependence alters synaptic connectivity of PVT inputs onto $NAc^{PV\text{-}INs}$ using slice electrophysiology and optogenetic stimulation of PVT terminals to evoke excitatory postsynaptic currents (EPSCs) onto $NAc^{PV\text{-}INs}$. CIE significantly reduces the amplitude of optically-evoked AMPAr EPSCs and AMPA/NMDA ratios in $NAc^{PV\text{-}INs}$. Additionally, behavioral stressors, TMT and quinine, reduce alcohol-seeking in non-dependent mice, and the ability of these behavioral suppressors to reduce alcohol seeking is abolished in dependent mice. In vivo optogenetic inhibition of PVT-NAc blocks the ability of these suppressors to reduce seeking, while activation is sufficient to reduce seeking on its own, and is no longer effective after induction of dependence. Collectively, we find that this midline thalamo-striatal circuitry is sensitive to stressors and provides a feedforward brake on alcohol seeking that is disrupted by alcohol dependence, which significantly disrupts the functional activation and synaptic connectivity of PVT-$NAc^{PV\text{-}IN}$ circuitry to drive excessive alcohol seeking.

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S12
Substance P projections from the paraventricular nucleus of the thalamus to the nucleus accumbens and central amygdala: a potential mediator of alcohol consumption following social defeat stress

Lauren Beugelsdyk, Ellie Decker Ramirez, Komal Patel, Anthony Sego, Jesse Schank

The Neurokinin-1 receptor (NK1R) is the preferential receptor for the neuropeptide Substance P (SP), and has been investigated clinically and preclinically as a therapeutic target for Alcohol Use Disorder. The paraventricular nucleus of the thalamus (PVT) sends SP innervation to the nucleus accumbens (NAc) and central amygdala (CeA), two regions in which the NK1R is notably involved in alcohol and/or stress-related behaviors. Particularly, NK1R in the NAc mediates behavioral responses to Social Defeat Stress (SDS), a rodent model of chronic stress that can induce escalated alcohol consumption and depressive-like phenotypes. We have shown that chemogenetic inhibition of SP inputs to the NAc decreases post-SDS alcohol consumption, regardless of whether the inhibition occurred during SDS or during the post-stress alcohol consumption. Conversely, chemogenetic activation of these inputs increases alcohol consumption even in the absence of stress. We additionally examined neuronal activation following SDS within each brain region that innervates the NAc with SP, and found that PVT-NAc projections are preferentially activated by SDS. Therefore, we predict that circuit-specific chemogenetic inhibition of PVT-NAc SP projections following SDS will similarly reduce post-stress alcohol consumption. Additionally, nearly 40% of the PVT-NAc SP neurons also collateralize to the CeA, a region where the NK1R mediates alcohol seeking and stress-induced reinstatement. Current experiments are examining if these NAC + CeA projecting SP neurons are the same as those activated by SDS. The present findings indicate that PVT SP projections, particularly to the NAc and CeA, may be an important mediator of stress-induced escalation in alcohol consumption.

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S13
Alcohol dysregulation of adaptive estrogen signaling in the limbic thalamus

Kristen Pleil, Jacqueline Welday, Irena Pigulevskiy, Marta Melis, Lorraine Gudas, Kathy Grant

Neurons in the paraventricular thalamus (PVT) have varying afferent/efferent circuitry and molecular profiles across the anterior-posterior axis that confer differential roles in behavior. We have shown that the anterior and posterior PVT (aPVT, pPVT) differentially regulate binge alcohol drinking and stress responsivity in a sex-dependent manner, and the excitability of BNST-projecting PVT neurons and downstream glutamate release are sensitive to chronic alcohol in rodents and monkeys, promoting further drinking. We have also shown that estrogen enhances excitatory synaptic transmission at these synapses, enhancing binge drinking in females when ovarian-derived estrogen levels are high. Multiple labs recently showed that estrogen receptor alpha (ERα) is a marker for a large subpopulation of pPVT neurons based on molecular profile. As a broad transcription factor for synapse and excitability-related genes, we posit that ERα transcriptionally regulates specific pPVT projection populations to regulate adaptive behaviors including anxiety/mood states and risk-taking behavior, and that chronic alcohol disrupts these behaviors via aberrant estrogen tone and signaling in the pPVT. We found that ERα is densely expressed in BNST- and NAc-projecting PVT neurons.

Further, both estrogen state in naïve females, and alcohol drinking in both sexes, decreased the intrinsic excitability of persistent-firing pPVT neurons. Surprisingly, chronic alcohol increased estrogen synthesis in the liver and estrogen levels across the liver-blood-brain axis, altogether suggesting that alcohol-induced estrogen synthesis in the liver confers aberrant estrogen signaling in the pPVT.
Current experiments are examining the mechanisms for estrogen modulation of pPVT circuits and aberrant hepatic steroid hormone metabolism in mice and monkeys.

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S14
Genetic and physiological adaptations in the nucleus reuniens of the thalamus as drivers of aberrant alcohol- and stress-related behaviors in mice

Patrick Mulholland, Kathy L. Linquist, Jennifer A. Rinker

Excessive alcohol drinking produces cognitive deficits and negative affective behaviors that hinder treatment efforts and contribute to higher risk for relapse. While some regions important for cognition and anxiety have been studied extensively, other key brain regions controlling these behaviors are understudied in the alcohol field. The nucleus reuniens (RE) is a higher-order midline thalamic nucleus that is a nexus for integration of cortical and subcortical signaling and is functionally and transcriptomically distinct from other thalamic regions. The RE projects to brain regions that support working memory and attention and has also been implicated in control of negative affective behaviors. However, there is a substantial gap in our understanding of alcohol's influence on RE functional adaptations and the RE's role in controlling alcohol-related behavioral deficits. In mice, we found that chronic intermittent ethanol (CIE) exposure produced cognitive deficits and altered approach-avoidance behaviors. Analysis of the RE transcriptome showed divergent gene expression changes in male and female alcohol dependent mice for processes related to cellular physiology and the extracellular matrix. Electrophysiological validation studies of RE neuron physiology showed adaptations in cell firing, depolarization of the RMP, and decreased amplitude of IPSCs in CIE mice.
Chemogenetic inhibition of the RE rescued working memory deficits and anxiety-like behaviors in dependent mice while also reducing drinking only in mice with a high drinking phenotype. Thus, these findings demonstrate that alcohol dependence produces genetic and physiological adaptations in RE neurons that facilitate deficits in alcohol- and stress-related behaviors.

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S15
Frontocortical thalamic inputs are selectively vulnerable to adolescent alcohol consumption in a mouse model of ADHD

Michael C. Salling, Sukanya Gakare, Hannah Jarrell, Grace Qian, Faith Maxwell, Hernan Mejia-Gomez

Longitudinal clinical neuroimaging studies separately indicate that individuals with attention deficit hyperactivity disorder (ADHD) and heavy alcohol consumption during adolescence have altered development of the prefrontal cortex (PFC) and associated deficits in impulsivity and emotional regulation. Many of the structural and behavioral outcomes associated with ADHD and adolescent alcohol have been recapitulated in preclinical rodent models permitting mechanistic inquiry. The major thalamic projection target of the PFC is the mediodorsal thalamus (MdT) and we will present data demonstrating that adolescent alcohol consumption selectively reduces glutamatergic transmission and plasticity in PFC^{MdT} neurons as well as spine density in apical and basal PFC^{MdT} dendrites in male and female mice. Comprehensive behavioral characterization finds that adolescent alcohol mice show increased impulsivity, deficits in spatial object recognition, and reduced cognitive processing. Selective PFC deletion of Latrophilin-3 (Lphn3), a cell adhesion GPCR involved in glutamatergic synapse maintenance and a risk gene variant for ADHD, show similar reductions in glutamatergic transmission and spine density in PFC^{MdT} projections, however, behavioral characterization demonstrates increased anxiety-like behavior selectively in Lphn3 PFC^{KO} males following adolescent alcohol consumption. Collectively, these data reveal unique contributions of adolescent alcohol and Lphn3 to impulsive and anxiety-like behavior that may converge on mediodorsal thalamic inputs from the PFC. Selective D1 agonism helps normalize glutamatergic transmission in PFC^{MdT} neurons likely through a presynaptic mechanism and may serve as a treatment strategy for alleviating associated cognitive and anxiety phenotypes.

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Symposium IV
Effects of ethanol and its metabolites on genes, ion channels, and bioenergetics: from molecular to organismal perspective
Chairs: Paul Slesinger and Alex Dopico
S16
Why Some Resist: Epigenetic Control of Resilience to Compulsive Alcohol Drinking

Daniel DaSilva

Alcohol Use Disorder (AUD) remains a major public health challenge, with rising mortality and limited treatment options. A hallmark of severe AUD is compulsive alcohol drinking, persistent consumption despite negative consequences, reflecting a breakdown in decision-making and behavioral flexibility.
Yet, not all individuals exposed to chronic alcohol develop this maladaptive phenotype, suggesting the presence of active resilience mechanisms. Defining the molecular and cellular basis of this resilience could uncover new therapeutic targets.
Our group identified an epigenetic program within the dorsomedial striatum (DMS) that supports resilience to compulsive alcohol use. Using an operant self-administration paradigm coupled with punishment (quinine adulteration or foot shock), we stratified genetically identical mice into punishment-sensitive (resilient) and punishment-resistant (compulsive-like) subgroups. Single-nucleus RNA-seq and cell-type–specific TRAP-seq revealed a distinct transcriptional profile in dopamine D1 receptor–expressing medium spiny neurons (D1-MSNs) of resilient mice, marked by downregulation of dopamine receptor signaling and upregulation of NAD-dependent histone deacetylase activity.
Among these, Sirtuin 7 (Sirt7) emerged as a key molecular hub: it was selectively upregulated in D1-MSNs of resilient mice and statistically mediated the relationship between chromatin remodeling and synaptic gene expression. Bayesian network analysis further positioned Sirt7 upstream of critical synaptic genes implicated in behavioral control. These results support a model in which Sirt7 modulates histone acetylation to constrain synaptic plasticity and promote behavioral flexibility under aversive conditions. Together, our findings highlight a novel epigenetic mechanism of resilience in AUD, bridging chromatin dynamics with circuit-level adaptation and pointing toward more targeted interventions for compulsive alcohol use.

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S17
Selective activation of GIRK1 potassium channels reduces behavioral and brain responses to ethanol in mice

Paul Slesinger

Alcohol use disorder (AUD) is a chronic relapsing condition with limited pharmacological treatment options. Ethanol modulates neuronal excitability in part through activation of G-protein-gated inwardly rectifying potassium (GIRK/Kir3) channels, which dampen neuronal activity in reward- and stress-related circuits implicated in AUD pathophysiology. In this study, we investigated the therapeutic potential of GiGA1, a selective small-molecule activator of GIRK1-containing channels, in mouse models of ethanol intoxication. GiGA1 administration prevented ethanol-induced conditioned place preference (CPP) acquisition in both male and female mice, attenuated ethanol-induced locomotor stimulation in females. In a self-administration model of alcohol use, GiGA1 also significantly reduced voluntary ethanol intake and blood alcohol concentrations, even when administered after mice showed high preference and consumption of ethanol, without affecting drinking water. In contrast, Baclofen, a GABAB receptor agonist that indirectly activates GIRK channels, decreased ethanol consumption but failed to block ethanol-CPP, suggesting a mechanistic distinction and broader efficacy of direct GIRK1 activation. Whole-brain cFos mapping of neuronal activity revealed that GiGA1 blunted ethanol-induced neuronal activation in several AUD-relevant brain regions, including the central amygdala, paraventricular thalamus, paraventricular hypothalamus, and

Edinger–Westphal nucleus. These findings demonstrate that pharmacological activation of GIRK1- containing channels modulates key neural circuits involved in ethanol reward and intake, supporting GiGA1 as a promising lead compound for targeted AUD therapy.

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S18

Reduced ethanol drinking and glycine receptor function in the nucleus accumbens with age

Luis G. Aguayo, Carlet Gallegos, David Hernandez Castillo, Alejandra Guzman Castillo

The nucleus accumbens (nAc) is a key region of the reward system, and its principal neurons express glycine receptors (GlyR). These inhibitory ligand-gated ion channels modulate neuronal excitability and ethanol consumption. Patch clamp recordings showed that the amplitude of the glycine-activated current decreased with age (3-12 months). Additionally, the sensitivity of GlyRs to ethanol was reduced in 12-month-old mice. Data derived from immunohistochemistry experiments in aging Drd1a-tdTomato mice shows a selective reduction of alpha subunits in $D1^+$ MSNs. Additional analysis of mRNA levels in $D1^+$ and $D1^-$ neurons previously separated by fluorescence-activated cell sorting (FACS) revealed that a1 and a2, but not a3 subunits, decreased with age. Photometric analysis of intracellular calcium dynamics in MSNs using GCaMP6s showed a reduced effect of ethanol on overall excitability with ethanol and strychnine, which agrees with a reduced presence of GlyRs in the accumbens. The aged mice showed decreased levels of drinking using the drinking in the dark protocol and loss of conditioned place preference to ethanol at 6 months, indicating that CPP is highly dependent on brain aging.
In conclusion, the expression of a1 and a2 subunits in nAc were reduced with age. The reduction in these subunits was well correlated with a decrease in the sensitivity of functional GlyRs to ethanol and drinking, which are known to depend on the receptor conformation.

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S19

Cerebral artery smooth muscle BK channels are functional targets of ethanol and the neurosteroids pregnenolone and progesterone

Alex Dopico

Central neurons critically rely on aerobic metabolism and thus proper blood flow, which is determined by the smooth muscle (SM) tone and diameter of cerebral arteries. Cerebral artery diameter is regulated by circulating, endothelial and local factors, including neurosteroids, yet ultimately determined by ion channels in cerebrovascular SM that serve as effectors of endogenous signals and drugs of misuse. Thus, activation and inhibition of voltage/calcium-gated potassium channels of large conductance (BK) in cerebral artery SM lead to vasodilation and vasoconstriction, respectively. We previously showed that ethanol at concentrations reached in circulation upon binge drinking evoked cerebral artery constriction via BK inhibition. We also documented that the neurosteroids pregnenolone and progesterone, with significant roles in alcohol use disorders, caused BK inhibition-cerebrovascular constriction and BK activation-cerebrovascular dilation, respectively. Here, I will present published and unpublished results from our laboratory identifying: (a) Tyr450 in the BK-channel forming subunit as a critical residue that enables pregnenolone to inhibit BK and cause cerebrovascular constriction; (b) several residues in the BK-accessory beta1 subunit that enable progesterone to activate BK and cause cerebrovascular dilation; (c) Ser160 in this accessory subunit as a critical residue that enables ethanol to inhibit BK and cause cerebrovascular constriction. The interactions among these modulators on BK function and on cerebral artery diameter both ex vivo and in vivo will also be presented. Our work advances that SM BK is a common effector of neurosteroid and ethanol actions on brain arteries, yet each ligand acts through different BK subunits and molecular sites.

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Symposium V

Insular dynamics in stress and alcohol use: a cross-species perspective on craving, compulsion, and abstinence

Chair: Samuel Centanni

Discussant: Elizabeth Goldfarb

S20

Stress-induced sensitization of insula activation predicts alcohol craving and alcohol use in alcohol use disorder

Patrick Bach, Judith Zaiser, Sina Zimmermann, Tatjana Gessner, Sabine Hoffmann, Sarah Gerhardt, Oksana Berhe, Nina Kim Bekier, Martin Abel, Philipp Radler, Jens Langejürgen, Heike Tost, Bernd Lenz, Sabine Vollstädt-Klein, Jan Stallkamp, Clemens Kirschbaum, Falk Kiefer

The interplay between stress and alcohol cues represents a critical mechanism underlying relapse vulnerability in alcohol use disorder (AUD). However, the neurobiological processes mediating their interaction remain poorly understood.
The talk will present data of a recent randomized controlled neuroimaging study investigating the effects of psychosocial stress on neural alcohol cue reactivity and addictive behaviors in 91 individuals with AUD. Neural alcohol cue reactivity was assessed using functional magnetic resonance imaging (fMRI) at baseline and during a second session following randomization to psychosocial stress, matched control condition, or physical exercise control. Neural cue-reactivity, cortisol levels, alcohol craving, and 12-month follow-up alcohol use data served as outcomes.
Compared to both control conditions, psychosocial stress elicited higher alcohol cue-induced activation in the left anterior insula (familywise error-corrected $p<.05$) and a stress- and cue-specific dynamic increase in insula activation over time ($F=2.143$, $p=.007$), which was more pronounced in individuals with stronger stress-induced cortisol release ($r=0.310$, $p=.016$). Importantly, cue-induced insula activation was positively correlated with alcohol craving during fMRI ($r=0.262$, $p=.032$) and alcohol use during follow-up ($r=0.218$, $p=.046$).
Findings indicate a stress-induced sensitization of cue-induced activation in the left anterior insula as a neurobiological correlate linking psychosocial stress to alcohol craving and consumption in AUD, highlighting the insula's critical role as a convergence point for stress and reward processing in addiction neurobiology. The talk will close with a discussion on how stress-associated changes in salience attribution to alcohol cues could be a potential mechanism that promotes goal-directed alcohol-seeking behavior through enhanced insula engagement.

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S21

The insular cortex: the gateway from impulses to compulsion

David Belin

Failure to adaptively cope with stress contributes to the development of several neuropsychiatric disorders, including obsessive–compulsive disorder (OCD) and alcohol use disorder. Preclinical studies using schedule-induced polydipsia (SIP) as a model of coping behaviour have revealed that while adjunctive drinking transiently reduces stress, some vulnerable individuals need alcohol to develop such a coping response, while others develop hyperdipsia, a compulsive form of SIP. A high impulsivity trait confers vulnerability to this shift, which depends on noradrenergic mechanisms and the anterior insula (AI). Highly impulsive rats exhibit reduced thickness of and cellular plasticity in the AI. Bilateral AI lesions reduce impulsivity and prevent the development and expression of hyperdipsia, establishing the AI as a neural substrate of impulsive–compulsive vulnerability. The role of AI in alterations in Decision-making further delineates the contribution of AI to the perpetuation of compulsive behaviours. Functionally disconnecting the Prefrontal cortex from the AI impairs decision making. These results reveal that the AI, interacting with corticostriatal networks, mediates the transition from impulsivity to compulsion, offering mechanistic insights into vulnerability and novel intervention targets for compulsive disorders, including alcohol use disorder.

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S22

The distinct roles of the S1-insula circuit in alcohol drinking and negative affect in abstinence

Tatiyana L. Adkins, Amanda L. Salazar, Jincy R. Little, Ellen C. Howard, Samuel W. Centanni

Sensory processing assigns salience to environmental and internal stimuli, shaping behavior through learned associations. In alcohol use disorder (AUD), this process is dysregulated, causing sensory cues to perpetuate excessive drinking and negative affect in abstinence. Stress is an omnipresent influence on AUD, yet the mechanisms driving stress-induced sensory dysregulation remain poorly understood. The primary somatosensory cortex (S1) encodes tactile, thermal, proprioceptive, and nociceptive inputs, and projects to higher-order regions involved in motor and emotional processing. One target is the insula, a hub for interoceptive integration and affective regulation. This talk presents new data
implicating the S1-insula circuit in alcohol drinking and negative affective states in abstinence. First, we mapped the larger S1-insula circuitry in mice. Insula neurons receiving S1 projections extend into the extended amygdala, implicating this projection in emotional processing. Furthermore, S1-insula neurons collateralize to motor and sensory processing regions. Using chemogenetics, fiber photometry, and two mouse models of AUD- binge-like drinking and chronic drinking with forced abstinence- we demonstrate that the S1-insula circuit is selectively recruited during ethanol drinking and aversive behaviors. Chronic ethanol disrupts this circuit's engagement, suggesting a maladaptive shift in sensory-affective integration. S1-insula neurons show both immediate and delayed activity increases in response to an ethanol lick, indicating temporally distinct roles. These findings reveal a unique cortico-cortical mechanism by which somatosensory signaling modulates cue reactivity and internal affective states in AUD. This work identifies a dynamic intersectional point of stress and alcohol-related behavior, identifying a potential circuit-level target for diagnostic and therapeutic strategies.

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S23

Sex differences in incubation of craving for alcohol-associated cues: a role for the insular cortex?

Christina Perry, Tom Ferella, Laisa De Siquiera Umpierrez, Mia Lavee, Rhys Vorillas, Tracey Tran, Ashleigh Lawrence, Jennifer Cornish

Incubation of craving refers to increased sensitivity to drug-associated cues over a period of abstinence. In rodents, this is modelled by an increase in cue-elicited drug-seeking, however few studies have examined this with alcohol. We recently showed, in male rats, not only that incubation of craving occurred for alcohol-associated cues, but that it could be prevented if rats were allowed access to running wheels across abstinence. Here I will report data from two follow-up experiments. Experiment 1 investigated corticostriatal pathways recruited during incubation. Male and female rats injected with a retrograde tracer aimed at specific striatal loci, were trained to lever-press for alcohol. Cued alcohol-seeking was tested before or after 4 weeks of abstinence, and fixed post-mortem brains were processed for activity-markers in back-labelled neurons. Incubation was evident in both males and females, and was associated with recruitment of insular cortex to dorsomedial striatum projecting neurons. Experiment 2 investigated sex differences in the exercise effect. Male and female rats were trained as for 1, and half had access to running wheels across abstinence. As previously, exercise reduced incubation for males, however in females there was no reduction. These data are the first to show recruitment of specific cortico-striatal pathways during incubation of craving for alcohol, and further show important sex differences in relapse-preventing effects of exercise. **Conclusion:** Although exercise shows promise as an adjunctive treatment for alcohol use disorder, further investigation into why it was ineffective in females is essential, both to understand the mechanism and for effective translation.

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Symposium VI

Dynorphinergic / kappa-opioid receptor-regulated cortical and limbic circuitry at the intersection of alcohol and stress

Chairs: Brendan Walker and Ethan Anderson

Discussant: Rainer Spanagel

S24

Adolescent social isolation enhances stress and alcohol vulnerability via opioid gene expression changes in a sex-dependent manner

Loredana Maria Losapio, Adana Keshishian, Laura Rullo, Sofia Vellere, Massimo Ubaldi, Laura Soverchia, Sanzio Candeletti, Patrizia Romualdi, Roberto Ciccocioppo, Esi Domi

Chronic stress during developmental periods leads to altered functional connectivity and increases vulnerability to anxiety disorders and alcohol addiction in adulthood. Early-life stress may disrupt the maturation and function of brain regions involved in emotion and reward processing. These alterations may, in turn, heighten susceptibility to substance use by affecting reward circuitry. Specifically, dysregulation of the the dynorphin (DYN)/κ-opioid receptor (KOR) pathway, has been proposed as a key mediator of these long-term effects. However, the sex-specific role of the endogenous opioid system in mediating these outcomes remains poorly understood.
To investigate the long-term neurobiological effects of adolescent social isolation, male and female Wistar rats were under grouped housing (GH) or social isolation (SI) conditions during adolescence. In adulthood, animals were tested for anxiety-like and alcohol-related behaviors. At PND60, gene expression analysis of DYN, KOR and μ-opioid receptor (MOR) was performed in the prelimbic cortex (PrL) and amygdala, brain areas involved in emotional processing, stress-coping behavior, and reward.
SI rats of both sexes exhibited increased anxiety-like behaviors relative to GH controls, while SI females demonstrated a greater vulnerability to alcohol use disorder (AUD)-related behaviors. At the molecular level, adult SI females showed a significant upregulation of DYN and KOR, but not MOR, mRNA expression, suggesting sex-specific transcriptional adaptations to adolescent social isolation. Collectively, these findings underscore the enduring, sex-dependent impact of adolescent social isolation on stress- and alcohol-related behaviors, with females displaying heightened susceptibility.

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S25

Kappa opioid receptor modulation of BLA inputs to the BNST regulates social stress escalated alcohol intake

F. Paliarin, E. Dore, S. Mirza, L. Finlay, T. Nguyen, E. Weiser, C. Duplantis, R. Maiya

Social stress can drive escalated alcohol consumption and increase the risk of relapse to alcohol seeking. The biological underpinnings of this are not clear and must be elucidated to facilitate identification of therapeutic targets. Social stress has been effectively modeled in animals through social defeat stress (SDS) procedures. Our results show that repeated SDS enhances alcohol consumption and preference in both male and female C57BL/6J mice. The Dynorphin/Kappa opioid receptor (Dyn/KOR) system plays as a key mediator of stress effects. Systemic administration of the selective KOR antagonist norBNI significantly and selectively reduced alcohol consumption in both male and female stressed mice but not in unstressed controls. Chemogenetic activation of KOR expressing neurons in the BLA (BLAKOR) in Oprk1-Cre mice attenuated SDS-escalated alcohol consumption in males. KOR antagonism as well as chemogenetic activation of BLAKOR terminals in the BNST attenuated stress-escalated alcohol consumption in both sexes implicating this pathway in regulating SDS-escalated alcohol intake. Consistent with these results, KOR deletion in the BLA also attenuated social stress escalated alcohol consumption in females. We next examined sources of Dyn in the BNST that are recruited by SDS. We found increased *pDyn* expression in the dorsal raphe nucleus (DRN) and enhanced stress-induced activation of BNST-projecting DRN^{Dyn} neurons, identifying them as a likely source of Dyn recruited by SDS. Future experiments will determine the impact of KOR deletion in the BLA-BNST pathway and test the causal role of DRN^{Dyn} neurons in SDS-escalated alcohol intake.

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S26

Corticolimbic dynorphinergic / kappa-opioid receptor circuitry underlies dysphoria cue-induced escalation of alcohol self-administration

Brendan M. Walker, Gengze Wei, Maddison Gostin, Gaetan Lepreux

Alcohol use disorder (AUD) diagnoses are dramatically increased in those with post-traumatic stress disorder (PTSD) compared to the regular population. Dynorphin (DYN) / kappa-opioid receptor (KOR) system dysregulation can contribute to AUD-related behaviors by increasing dysphoria, which has implications for trauma-related psychopathologies such as PTSD, and can lead to excessive self-administration of alcohol to alleviate the dysphoric states (i.e., self-medication). To evaluate this in an AUD / PTSD comorbidity rodent model utilizing dysphoria cues, we pharmacologically validated a role for basolateral amygdala (BLA) KORs in dysphoria cue-induced excessive alcohol consumption. Phenotypic evaluation of male and female transgenic floxed *Oprk1* (KOR gene) mice in the dysphoria cue-induced alcohol escalation model showed that female, compared to male, floxed *Oprk1* mice had a shift to the left in the dysphoria cue-induced alcohol escalation dose-response curve. Subsequently, we leveraged Cre-Lox technology to inducibly excise the *Oprk1* gene in the BLA after dysphoria-like KOR agonist / cue conditioning with the goal of rescuing cue-induced excessive alcohol consumption. When *Oprk1* was inducible excised in the BLA, dysphoria cue-induced escalation of alcohol self-administration was ameliorated in both sexes. Next, retrograde Cre-dependent viral constructs in Pdyn::Cre mice identified multiple corticofugal *Pdyn*+ (DYN gene) projections to the BLA. When assessed within the dysphoria cue model, dissociable activation profiles were present among the BLA-projecting cortical sites and could be reversed via chemogenetic manipulations. These data support focusing on the DYN / KOR system as a therapeutic target for AUD / trauma comorbidity in a manner relevant for public health.

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S27

Prefrontal cortex bidirectionally routes stimulus valence to the periaqueductal gray via glutamatergic and dynorphinergic mechanisms

Cody Siciliano, Lindsay M. Cain, Zahra Z. Farahbakhsh, Zev E. Jarrett, Jose C. Zepeda, Brad A. Grueter

Convergent preclinical and clinical evidence demonstrate that activity patterns in medial prefrontal cortex (mPFC) neurons projecting to the dorsal periaqueductal gray (dPAG) are a prodromal marker of alcohol use disorder and putative causative agent mediating punishment insensitivity. Though the mPFC→dPAG is thought to be entirely glutamatergic, human neuroimaging suggests that two regulatory mechanisms between the PFC and PAG, one excitatory and one inhibitory, differentially contribute to alcohol use disorder pathophysiology. Here, in C57BL/6J mice, we used single cell calcium imaging of dPAG neurons with simultaneous optogenetic activation of local mPFC→dPAG terminals to photoidentify functionally connected neurons downstream of the mPFC→dPAG circuit. Observation of dPAG activity revealed that valence coding observed in upstream mPFC projection neurons is transferred to a subset of in-network dPAG cells. Optogenetic activation of mPFC→dPAG resulted fast excitation followed by a slow-onset inhibitory effect in the dPAG. Single cell RNA sequencing of mPFC→dPAG projectors revealed abundant expression of *PDYN*, which encodes the dynorphin precursor protein preprodynorphin. *PDYN* was enriched in mPFC→dPAG as compared to other gene markers for inhibitory neuromodulators as well as in comparison to neighboring mPFC projection populations. We found that kappa opioid receptor activation reduces the frequency of spontaneous excitatory post-synaptic currents in dPAG neurons, mirroring the effect of mPFC activation, while blockade occluded effects of mPFC→dPAG photostimulation on spontaneous event frequency. Taken together, this work implicates dynorphin release from mPFC→dPAG neurons as a potential mechanism by which this circuit coordinates motivated behaviors and alcohol drinking.

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S28

A Methyltransferase Knockdown in the Accumbens Increases Excitability and Reduces Stress-Escalated Ethanol Drinking in Mice

Ethan M. Anderson

A common mechanism that regulates both stress-sensitivity and alcohol use is epigenetic regulation. One epigenetic modifier implicated in alcohol use disorder (AUD) is G9a, a histone methyltransferase, downregulated by alcohol in the nucleus accumbens (NAc). Here we investigated if there is a cell-type specific effect of NAc G9a, how G9a alters the NAc transcriptome, and if this epigenetic modifier alters neuronal excitability. Since the dynorphin/kappa opioid receptor (Dyn/KOR) system plays a prominent role in stress/ethanol-related behaviors and dynorphin is present in a major subset of NAc neurons (NAc^{Dyn+}), we hypothesized that G9a acts selectively through NAc^{Dyn+} neurons to alter stress-potentiated drinking. We tested this by injecting a novel cre-dependent AAV virus (AAV-DIO-shG9a) into the NAc of both dynorphin-cre and enkephalin-cre mice. Control Dyn-cre mice exhibited stress-potentiated drinking induced by systemic injection of the KOR agonist U50,488, but not when G9a was reduced in experimental mice. In contrast, we found no effect of G9a in NAc^{Enk+}. A transcriptomic analysis revealed that NAc G9a alters genes associated with excitability, so we next used slice physiology to measure changes in current-evoked spiking activity and rheobase. We found that a G9a knockdown led to an increase in NAc intrinsic excitability, likely due to an epigenetic change in potassium channel expression. Combined, these results suggest that the effects of NAc G9a on stress-potentiated drinking are mediated by altering the excitability of NAc^{Dyn+} neurons. Thus, targeting G9a, specific potassium channels, and/or NAc^{Dyn+} neurons could help reduce stress-escalated alcohol drinking in patients with AUD.

https://doi.org/10.1016/j.alcohol.2026.01.043

Symposium VII

Modulating central cholinergic activity: implications for therapeutic potential in treatment of alcohol and stress related disorders

Chairs: Howard Becker and Andrew Lawrence

S30

Neurotoxic effects of chronic ethanol on cholinergic interneurons in the dorsomedial striatum

Armando Salinas, Logan E. Slade, Charles C. Levy, Jacob T. Mitcham, Morgan Schichtel

Alcohol use disorder (AUD) has severe adverse health, social, and economic impacts over $240 billion annually in the US. There are three FDA approved treatments for AUD, though each has limited efficacy. Thus, a better understanding of neurobiological mechanisms contributing to AUD is necessary to develop new treatments. One possible target is the cholinergic system. Indeed, the nicotinic acetylcholine receptor agonist, varenicline, has shown limited promise for the treatment of AUD. This suggests a potential cholinergic deficit in AUD. Notably, animal models with ablated dorsal striatal cholinergic interneurons (CINs) exhibit deficits in cognitive flexibility similar to AUD patients. Thus, we posit that chronic alcohol leads to striatal cholinergic signaling deficits that contribute to AUD. To test this, we used the chronic intermittent ethanol vapor treatment (CIE) model in mice expressing an acetylcholine (ACh) biosensor in dorsal striatum. We found that CIE-treated mice had depressed ACh release compared to control mice in dorsomedial, but not dorsolateral, striatum. To determine the cause of this deficit, we performed stereological cell counts of striatal cholinergic interneurons in control and CIE mice. In accord with our ACh release data, we found that CIE mice had a significant decrease in CINs in the dorsomedial but not dorsolateral striatum. We then increased striatal ACh levels and observed decreases in ethanol intake relative to control mice.

Altogether, our data show that chronic ethanol has a specific neurotoxic effect on dorsal striatal cholinergic signaling in a subregion specific manner that may contribute to AUD related behaviors.

https://doi.org/10.1016/j.alcohol.2026.01.044

S31

Adolescent Intermittent Ethanol Exposure Disrupts Neurotrophin Balance to Drive Cholinergic and Behavioral Dysfunction

Lisa Savage

Adolescent intermittent ethanol (AIE) exposure and the subsequent withdrawal period alter the balance between pro and mature neurotrophins. These neurotrophin forms of nerve growth factor (NGF) regulate the survival and function of cholinergic neurons across the lifespan through TrkA and p75 neurotrophic receptors. Our recent findings show that inhibition of the $p75^{NTR}$-mediated degenerative pathway during AIE protects against ethanol-induced disruptions in ChAT/TrkA positive neurons, medial prefrontal cortical acetylcholine signaling, and attention-related behaviors. Moreover, post-AIE exercise restores cholinergic gene expression by reversing epigenetic suppression and reinstating behaviorally relevant acetylcholine activity. Together, these results highlight the remarkable plasticity of the forebrain cholinergic system and establish the $p75^{NTR}$/TrkA signaling balance as a critical determinant of alcohol-related neurotoxicity and recovery potential.

https://doi.org/10.1016/j.alcohol.2026.01.045

S32

Muscarinic M4 & M1/M4 Receptor Agonists for Schizophrenia, Historical Perspective & Current Status with implications for the treatment of alcohol use disorder

Anders Fink-Jensen

Muscarinic acetylcholine receptors, particularly the M1 and M4 subtypes, have emerged as promising targets in the treatment of schizophrenia, offering a novel approach beyond traditional dopaminergic antipsychotics. Historically, the therapeutic potential of muscarinic agonists was hindered by peripheral side effects and limited receptor selectivity. However, recent advances have led to the development of subtype-selective agonists and positive allosteric modulators (PAMs), enabling more precise modulation of central muscarinic activity. M4 receptor activation, in particular, has shown efficacy in reducing psychotic symptoms by indirectly modulating dopamine pathways, while M1 activation contributes to cognitive enhancement. The clinical effects of xanomeline, an M1/M4-preferring agonist, in combination with the peripheral anticholinergic trospium, in reducing both positive and negative symptoms of schizophrenia, have revitalized the interest in muscarinic therapeutics.
Beyond schizophrenia, there is growing interest in the role of muscarinic M1 and M4 receptors in addiction, particularly alcohol use disorder (AUD). Preclinical studies suggest that both M1 and M4 activation may reduce drug-seeking behavior by modulating reward circuitry. These findings imply a potential dual benefit of M1/M4-targeted therapies for individuals with comorbid schizophrenia and AUD. Initiation of clinical trials is underway, exploring these translational opportunities, which signals a shift toward mechanism-based pharmacotherapy in psychiatry. In summary, muscarinic M1 and M4 receptor agonists represent a promising frontier in the treatment of schizophrenia and may hold therapeutic value for AUD, particularly in patients with overlapping neuropsychiatric conditions.

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S33

M4 Muscarinic Acetylcholine Receptor Agonism Decreases Alcohol Drinking and Stress-Induced Alcohol Relapse in Mice

Howard C. Becker, Marcelo F. Lopez, Carrie Jones, Leigh C. Walker, Andrew J. Lawrence

A growing body of evidence has emerged implicating muscarinic cholinergic receptors (mAChRs) as novel and promising targets for treatment of alcohol use disorder (AUD). To extend results from human post-mortem tissue and rats, we examined whether similar changes in mAChR expression occur after chronic alcohol exposure in mice. Results from qPCR analysis indicated reduced *Chrm4* mRNA (but not *Chrm1* mRNA) expression in mouse striatum following four weeks of chronic intermittent alcohol vapor (CIE) exposure, further implicating an important role for the M4 AChR subtype. Subsequent studies were conducted to examine the effects of the M4-preferring agonist xanomeline and the M4 positive allosteric modulator (PAM) VU0467154 on alcohol consumption and stress-induced alcohol relapse in C57BL/6J mice. Xanomeline (5-30 mg/kg; ip.) significantly reduced home-cage limited access drinking, operant alcohol self-administration, and cue-induced relapse responding in a dose-related manner. Similarly, VU0467154 (1-10 mg/kg; ip.) significantly reduced CIE-related escalated home-cage drinking. Additionally, after establishing stable operant alcohol self-administration and then extinction responding, VU0467154 administration blocked the ability of a pharmacological stressor (0.0625 mg/kg yohimbine) and predator odor (TMT) exposure to trigger reinstatement of 'alcohol-seeking' behavior. Together, these results indicate that chronic alcohol exposure produces adaptations in M4 mAChR expression and M4 agonism is effective in reducing alcohol drinking and stress-induced alcohol relapse responding. Collectively, results across mice, rats, and humans provide compelling support for M4 mAChRs as a novel therapeutic target for treatment of AUD.

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Symposium VIII

Recent Advances in Animal Models of Alcohol Consumption Despite Negative Consequences

Chair: Jesse Schank

S34

Unveiling Genetic Determinants of Alcohol Addiction Vulnerability: Insights from Genetically Diverse Rat Models

Michelle R. Doyle, Paola Campo, Ran Qiao, Nurulain T. Zaveri, Abraham A. Palmer, Marsida Kallupi, Giordano de Guglielmo

Alcohol use disorder (AUD) impacts millions yearly, yet effective treatments are scarce. Variants in the CHRNA5-CHRNA3-CHRNB4 gene cluster, which encodes α3β4 nicotinic acetylcholine receptors (nAChRs), are associated with susceptibility to AUD. To address heterogeneous treatment responses, we investigated a precision medicine approach targeting α3β4 nAChRs in phenotypically distinct rat subgroups. Heterogeneous Stock (HS) rats underwent ethanol self-administration and dependence induction via chronic intermittent ethanol vapor. Using k-means clustering, we identified vulnerable and resistant phenotypes based on alcohol intake, motivation, compulsivity, tolerance, and withdrawal severity. A novel α3β4 nAChR partial agonist (0.2–0.8 mg/kg, s.c.) was evaluated for its effects on ethanol intake, motivation, reinstatement, and nicotine/saccharin self-administration. Electrophysiological studies assessed central amygdala (CeA) GABAergic activity and predicted CHRNA3 expression was correlated with ethanol consumption. Results showed distinct vulnerable and resistant phenotypes. The α3β4 nAChR agonist selectively reduced ethanol intake, motivation, and reinstatement in vulnerable rats, with minimal impact on resistant rats. It also decreased nicotine intake in vulnerable rats, sparing saccharin except at the highest dose. Electrophysiology revealed elevated CeA GABAergic tone in vulnerable rats, which the agonist normalized. CeA microinfusions confirmed its efficacy in vulnerable rats. Higher predicted CHRNA3 expression correlated with increased ethanol intake. These findings highlight that targeting α3β4 nAChRs effectively mitigates AUD-like behaviors in vulnerable phenotypes, driven by CeA mechanisms and CHRNA3 expression.
This precision medicine strategy, which integrates phenotypic and genetic profiling, supports personalized AUD treatments and merits clinical investigation.

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S35

Transcriptomic analysis of the central amygdala in aversion-resistant alcohol use: Sex differences

Leon Höglund, Estelle Barbier, Markus Heilig

Understanding the factors that confer vulnerability to alcohol addiction is essential for the development of effective therapeutic strategies. Biological sex is an important determinant in both the progression and treatment of alcohol addiction, highlighting the need to account for sex differences when designing interventions. Clinically, women are more likely to engage in heavy drinking as a maladaptive strategy to alleviate negative affective states, thereby increasing relapse risk, whereas men often report heavy drinking and relapse in response to positive emotions and social factors. Previous studies in our lab further indicate that, in males, levels of aversion resistant alcohol drinking, hereafter referred to as compulsive, correlate with motivation to obtain alcohol, while in females, this

behavior is predicted by basal corticosterone levels. The central nucleus of the amygdala (CeA) has been implicated as a critical region mediating compulsive drinking. To investigate the biological mechanisms underlying sex differences in this behavior, we performed single-nucleus RNA sequencing of the CeA from a large cohort of male and female rats trained in compulsive drinking. Samples from 72 animals, including compulsive, non-compulsive and foot shock-yoked controls, were submitted to extensive transcriptomic analysis including cell type specific differential expression analysis and co-expression network analysis. This analysis revealed transcriptomic differences across several cell types between compulsive and non-compulsive rats, with certain differences being sex-specific while others were shared across sexes.

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S36
Social isolation following alcohol consumption suppresses subsequent intake in mice

Jesse Schank, Lauren Beugelsdyk, Ellie Halpert, Swetha Pendela, Isabella Nguyen

Aversion-resistant alcohol consumption is often assessed using rodent models in which alcohol is paired with a negative stimulus such as adulteration with a bitter tastant or contingent footshock.
Continuation of alcohol intake under these conditions is thought to model alcohol use despite negative consequences in individuals with alcohol use disorder (AUD). However, individuals with AUD often experience negative consequences that are separated in time from their active alcohol drinking, and often impact their social life and interpersonal relationships. In our model, we trained mice to consume alcohol, and then exposed them to repeated social isolations following alcohol drinking sessions. We used the CD1 strain, as they have been found to be more responsive to social reward than C57BL6/J mice. We found that social isolation after drinking lead to decreased consumption relative to mice that were not isolated. This effect was observed in both males and females. There was considerable individual variability in this response with some mice suppressing more strongly than others. Alcohol consumption after social isolation correlated with consumption of quinine-adulterated alcohol, another major model of aversion-resistant drinking. Additionally, we observed increased Fos activation in specific brain regions of socially isolated mice, including the ventromedial prefrontal cortex and posterior insular cortex, which corresponds with patterns of activation that we have previously observed following quinine-alcohol drinking. We will next determine if interventions that induce aversion-resistance in other models, such as exposure to intermittent alcohol access or chronic stress, reduce sensitivity to social isolation-induced suppression of alcohol intake.

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S37
Exploring the neural mechanisms underlying addiction using improved models of aversion resistance

Elisabeth Glover

Current models of drinking despite negative consequences typically involve exposing subjects to aversive stimuli concomitant with consumption. However, aversive consequences associated with drinking are often variable and experienced separate from consumption. We tested the efficacy of two separate behavioral assays that present aversive consequences separate from drinking in an effort to more faithfully model the clinical condition. Adult Long Evans rats were trained on a delayed punishment decision making task (DPDT) during which a press on the safe lever resulted in immediate delivery of a single sucrose pellet, whereas a press on the punished lever resulted in immediate delivery of three sucrose pellets in addition to a one-second foot shock presented on a delay relative to reward delivery. A separate group of rats was trained on a newly developed unpredictable intermittent access (uIntA) drinking paradigm during which ethanol availability was paired with a discriminative stimulus presented randomly for unpredictable durations. After acquiring baseline data, rats in both paradigms were rendered dependent using a standard 14d chronic intermittent ethanol (CIE) vapor exposure paradigm. Daily behavioral testing continued through vapor exposure and into acute and protracted withdrawal periods. On the first withdrawal test session, rats undergoing uIntA were presented with a foot shock stressor concomitant with the ethanol-associated discriminative stimulus but in the absence of ethanol availability. CIE exposure produced paradigm-specific effects on aversion-resistant reward seeking. Our data suggest that while aversion-resistant reward seeking may precede ethanol dependence, chronic ethanol exposure also diminishes the salience of learned aversive stimuli.

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Symposium IX
Honoring Dr. Antonio Noronha
Adolescent binge drinking and stress induce adult AUD-like behaviors and changes in neurobiology
Chair: Fulton Crews
S38
Adolescent alcohol exposure produces alterations in pain processing in adulthood

Lawrence Chandler, Daniel Obray

Adolescent alcohol misuse is a major public health concern associated with numerous negative health outcomes. Although alcohol misuse and pain are known to be interrelated, their relationship during adolescence remains understudied. Emerging evidence suggests that repeated alcohol exposure during this developmental period can produce long-lasting increases in pain sensitivity that persist into adulthood. Using the Neurobiology of Adolescent Drinking in Adulthood (NADIA) rat model of adolescent intermittent ethanol (AIE) exposure, we found that adult rats previously exposed to AIE exhibit mechanical allodynia accompanied by hypofunction of prelimbic parvalbumin interneurons and increased excitability of prelimbic neurons projecting to the ventrolateral periaqueductal gray. These neural alterations suggest disrupted top-down modulation of pain sensitivity, providing a potential mechanistic link between adolescent alcohol exposure, persistent pain hypersensitivity, and increased vulnerability to alcohol misuse in humans.

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S39
Emerging Roles of Non-Coding RNAs in Adult Psychopathology Following Early-Life Alcohol Exposure

Subhash C. Pandey

Adolescent binge drinking significantly contributes to the development of alcohol use disorder and anxiety disorders later in life. Non-coding RNAs, including small non-coding RNAs (microRNAs) and long non-coding RNAs (lncRNAs), play essential roles in regulating gene expression and epigenetic changes related to synaptic plasticity. In this study, we report that adolescent intermittent ethanol (AIE) produces differential expressed miRNAs in adult amygdala. We observed an increase in miR-222 and a decrease in its target gene, Fos, as well as a reduction in Fos e2 RNA in the adult amygdala.
These alterations are linked to anxiety and alcohol drinking behaviors resulting from AIE in preclinical models. We extended these findings to humans, revealing that individuals with early-onset AUD (those who began drinking before 21) exhibited elevated levels of miR-222 alongside reduced levels of FOS and FOS e2 RNA in postmortem amygdala. We analyzed lncRNAs in the amygdala of both early and late-onset (began drinking after 21) AUD subjects compared to controls using qPCR. Our results revealed levels of H19, MALAT1, FAM225A, and FAM225B were increased, while levels of FTX, OLMALINC, and MIR3681HG decreased in AUD subjects. Correlation analyses indicated a significant positive correlation between AUDIT-C scores and levels of MALAT1 and FAM225B, as well as a positive correlation between FAM225B and alcohol consumption. Our data suggests that novel miRNAs and lncRNAs impacted by alcohol exposure may serve as promising therapeutic targets for treating AUD.

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S40
A Dorsolateral BNST-Parabrachial Nucleus Pathway Regulates Adolescent Alcohol-Induced Negative Affect in Females

L. Albrechet-Souza, T.A. Wills

Adolescent alcohol use is a strong predictor of alcohol use disorder (AUD) in adulthood and overlaps with a critical developmental window for the onset of

affective disorders. These comorbidities may contribute to problematic drinking and relapse risk, particularly in females. One proposed mechanism underlying AUD is negative reinforcement, where alcohol consumption temporarily alleviates negative emotional states during abstinence. We recently showed that chemogenetic stimulation of the dorsolateral bed nucleus of the stria terminalis (dlBNST) induces negative affect-like behavior in adult female mice with a history of adolescent intermittent ethanol (AIE) vapor exposure, but not in air-exposed females or in males. This phenotype was associated with heightened activation of calcitonin gene-related peptide (CGRP) neurons in the parabrachial nucleus (PBN), a region critical for maintaining homeostasis under stressful situations. Using a retrograde tracer combined with RNAscope, we identified direct dlBNST projections to the PBN arising from somatostatin- and prodynorphin-expressing neurons. Moreover, selective chemogenetic activation of dlBNST→PBN projections enhanced negative affect-like behavior in AIE-exposed females, but not in males. Together, these findings suggest that adolescent alcohol exposure produces sex-dependent adaptations in dlBNST-PBN circuitry. Specifically, adult females with a history of AIE may perceive novel and mildly anxiogenic contexts as highly threatening, engaging exaggerated defensive responses that could contribute to relapse vulnerability.

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S41

Proinflammatory HMGB1 and epigenetic contributions to persistent but reversible adolescent binge drinking- and stress-induced neuropathology.

R.P. Vetreno, F.T. Crews, H. Ross, S. de Castro, J. Castillo, M. Adelman

Adolescence is a conserved neurodevelopmental period characterized by maturation of the innate immune system and neurotransmitter systems marking the transition between childhood and adulthood. Adolescent binge drinking is common, and epidemiological studies suggest alcohol use disorder (AUD) is strongly associated with an adolescent age of drinking onset. Stress is also common in human adolescents, but the lasting consequences of stress exposure on brain development is poorly understood. Using the preclinical adolescent intermittent ethanol (AIE) model and the preclinical adolescent intermittent restraint stress (AIRS) model of adolescent adversity, we find that both induce similar neuropathology that persists into adulthood, including lasting high-mobility group box 1 (HMGB1)-mediated neuroimmune induction, disruption of neurotransmitter systems, and increased adult ethanol self-administration and related behavioral pathologies. Alcohol tolerance (i.e., an acquired reduction in acute alcohol responsivity) is a universally recognized key symptom of AUD, but the developmental mechanisms underlying acquisition of tolerance are poorly understood. We discovered that AIE confers lasting low alcohol responsivity (i.e., alcohol tolerance) in adulthood that is mimicked by HMGB1-mediated neuroimmune system activation using the inflammogen lipopolysaccharide. Adult treatment with the HMGB1 inhibitor glycyrrhizic acid reverses developmental acquisition of alcohol tolerance. In addition, treatment with glycyrrhizic acid and other anti-inflammatory compounds rescues persistent AIE- and AIRS-induced epigenetic suppression of cholinergic and serotonergic neuron phenotype as well as depression-like and anxiety-like behaviors in adulthood. Together, these data implicate HMGB1 proinflammatory neuroimmune signaling in increased risk for later AUD development and associated long-lasting neuropathology associated with adolescent binge drinking and adversity.

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Symposium X

Stress- and anxiety-sensitive brain circuits across species: Translational mechanisms of vulnerability for AUD

Chair: Marisa Silveri

S42

Distinct amygdala neuronal circuits regulating alcohol seeking and stress-induced drinking in mice

J. Suh, Q.C. Flanagan-Burt, B.K. Moon, A.L. Pasqualini, M.A. Zambrano, K.J. Ressler

The co-occurrence of PTSD and AUD presents major therapeutic challenges. The basolateral amygdala (BLA), a key brain region for associative learning and memory, is involved in context-dependent alcohol seeking and stress-induced escalation of alcohol drinking. Our studies revealed two distinct BLA neuronal subpopulations critical for these alcohol-related behaviors in mice.

First, we focused on Thy1-expressing BLA neurons, which are a subset of excitatory neurons projecting to the nucleus accumbens and prefrontal cortex, but not to the central amygdala. Using a conditioned place preference (CPP), we found that alcohol conditioning increased BLA-Thy1 neuronal activity. Inhibition of these neurons disrupted both the formation and recall of alcohol CPP. Furthermore, this context association and recall rely on BLA-Thy1 projections to the nucleus accumbens and prefrontal cortex, respectively, highlighting a projection-specific mechanism for alcohol seeking.

Second, we investigated a previously neglected population of CRF-expressing neurons (approximately 3% of BLA neurons), which exhibit high excitability. Projections from the insular cortex (IC), associated with interoception, showed augmented functional connectivity with BLA-CRF neurons following repeated social defeat stress (SDS). While activation of BLA-CRF neurons had no effect, inhibition of these neurons selectively prevented the stress-induced escalation of alcohol intake in SDS mice.

Together, our findings identify two molecularly distinct BLA circuits – Thy1 and CRF – that regulate separate, but intertwined, facets of alcohol-related behavior: one governing context-reward associations for alcohol seeking, and the other a top-down IC-to-BLA pathway driving increased drinking following stress. These insights offer a deeper understanding of neural circuit mechanisms underlying co-morbid PTSD and AUD.

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S43

Salience-regulation circuit inefficiency as a pre-existing vulnerability in youth prior to substance use onset

M.M. Silveri, J.E. Cohen-Gilbert, J.T. Sneider, H. Li, E.N. Oot, A.M. Seraikas, E.M. Schuttenberg, S.K. Harris, L.D. Nickerson

Adolescence is a sensitive developmental period when stress- and anxiety-sensitive brain circuits undergo rapid maturation. During this stage, salience and regulation networks support emotional flexibility, cognitive control, and stress responsivity. Neural inefficiency within these systems may create a latent vulnerability for substance use initiation, even in the absence of overt behavioral differences. Substance-naïve adolescents (ages 13–14; n=52) completed baseline neuroimaging and behavioral assessments and were followed prospectively for three years. Measures included arterial spin labeling (ASL) to quantify resting cerebral blood flow (CBF), functional MRI during an Emotional Go/No-Go task, the Behavioral Sensation Seeking Scale (BSSS), perceived stress (NIH Emotion Toolbox), and stress management (Bar-On Emotional Intelligence Youth-Version). At baseline, no group differences were observed in task performance, sensation seeking, perceived stress, or stress management. In contrast, adolescents who later initiated substance use exhibited higher resting perfusion in the left insula ($p=.016$), left caudal anterior cingulate ($p=.041$), and left caudal middle frontal gyrus ($p=.039$). During the Emotional Go/No-Go task, initiators showed weaker PFC–insula network strength for negative greater than neutral inhibition ($p=.038$). These findings support a pre-existing inefficiency model, in which salience-regulation circuitry, particularly left-lateralized frontal-insular hubs, is hyperactive at rest but fails to differentiate when emotional demands arise. Although behaviorally indistinguishable from peers, initiators demonstrate neural imbalances that may amplify stress sensitivity and confer risk for substance use initiation. Altogether, the results highlight salience–regulation inefficiency as a developmental risk phenotype, emphasizing the translational value of stress-sensitive neural circuits for understanding vulnerability to alcohol use disorder.

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S44

A circuit-based strategy to delineate novel targets to ameliorate negative affective behavior during alcohol abstinence

D.G. Winder, D.N. Adank, A. Taylor, Y. Quan, T. Freels, M.A. Doyle, J.R. Luchsinger

AUD is a highly heterogeneous disorder. In many cases, a significant contributing factor to the maintenance of AUD are the significant negative affective symptoms that can emerge during abstinence after periods on intake. We have previously demonstrated that projections from the mid-insula to the bed nucleus of the stria terminalis (BNST, insula^{BNST}) participate in driving alcohol

abstinence-associated rises in negative affective behavior in mice. To derive potential therapeutic strategies for diminishing the activity of this pathway, we have adopted a targeted circuit-guided approach. We performed a series of retrograde and anterograde circuit tracing experiments that revealed a large input from primary motor cortex (MOp) onto insula^{BNST} neurons. Further analysis showed parallel preferential innervation of somatostatin (SST) neurons in insula. We find that these SST cells inhibit insula^{BNST} neurons, that their activity is correlated with stress-induced movement, and that inhibition of their activity *in vivo* via chemogenetic approaches suppresses negative affective behaviors. Thus, the MOp input to insula and/or insular SST neurons are intriguing novel targets for mitigating negative affective behavior in alcohol abstinence.

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S45

Alterations in BNST connectivity during early abstinence in people with an alcohol use disorder

Jennifer Blackford, Nicole Zabik, Ozgun Ozalay, Katelyn Kelley, Marisa Silveri, Marshall Biven

Preventing relapse is a major barrier to long-term recovery from alcohol use disorder (AUD). Early abstinence is marked by heightened anxiety, a key driver of relapse and thus a critical intervention target. Animal studies show the bed nucleus of the stria terminalis (BNST) is central to alcohol withdrawal and relapse, yet translation to humans remains limited.

We investigated connectivity in a BNST network (amygdala, anterior hippocampus, anterior insula, hypothalamus, and ventromedial prefrontal cortex [vmPFC]) in people in early abstinence from an AUD (EA: n = 47, 32% F) and healthy controls (HC: n = 32, 50% F). The measures included structural connectivity (DWI), intrinsic functional connectivity (resting state fMRI), and task connectivity (fMRI unpredictable threat task). Linear mixed models were used to test for effects of group and sex in BNST connectivity ($p. < 05$).

Structural connectivity between the BNST and insula was significantly weaker in the EA group. Intrinsic connectivity between the BNST and both the amygdala and vmPFC was significantly weaker in the EA group. During the unpredictable threat task, BNST connectivity with the amygdala, insula, and hypothalamus was significantly stronger in the EA group. The BNST-hypothalamus connectivity differences were moderated by sex (EA F > HC F).

Early abstinence is characterized by weaker BNST structural and intrinsic functional connectivity and stronger BNST functional connectivity during unpredictable threat, highlighting the value of multi-modal approaches. These findings provide novel translational evidence for BNST alterations in early abstinence, with potential implications for relapse risk.

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Symposium XI

New insights into the neural effects of alcohol across the lifespan, from molecules to circuits

Chairs: Jeff Weiner and Dorit Ron

S52

Striatal FGF2-FGFR1 upregulation and altered microRNA profiles in compulsive-like alcohol drinking

Matar Levin-Greenwald, Segev Barak

The progression from controlled alcohol use to compulsive, aversion-resistant drinking is a hallmark of alcohol use disorder (AUD). Emerging evidence suggests that this transition involves neuroadaptations within striatal neurocircuits, yet the molecular underpinnings remain incompletely understood. Our previous work identified fibroblast growth factor 2 (FGF2) and its receptor FGFR1 as positive regulators of alcohol consumption via striatal dopaminergic pathways. Here, using a mouse model of compulsive alcohol drinking, based on intermittent access to 10% or 20% alcohol followed by quinine adulteration, we observed that *Fgf2* and *Fgfr1* mRNA expression increased throughout the mesocorticolimbic system selectively in mice that did not develop aversion-resistant drinking. In contrast, within the dorsomedial striatum (DMS), *Fgf2* and *Fgfr1* were upregulated in compulsive-like drinkers. Spatial analysis of FGFR1 protein expression revealed a shift toward the direct cortico-striatal pathway (D1-expressing medium spiny neurons, D1-MSNs) within the dorsal striatum of compulsive-like drinkers, implicating this circuitry in the expression of compulsive-like, aversion-resistant drinking behavior. Given that single-gene changes likely reflect broader regulatory shifts, we next searched for upstream molecular hubs. Small RNA sequencing of the DMS revealed robust downregulation of microRNA-9 (miR-9) and members of the miR-34 family in compulsive drinkers. Both miRNA families are predicted to regulate *Fgf2* expression, suggesting that their downregulation could influence FGF2-FGFR1 signaling and associated neuroplasticity. These findings identify parallel molecular adaptations in growth factor signaling and miRNA expression within striatal circuits linked to compulsive alcohol use, and point to potential post-transcriptional regulatory mechanisms that may contribute to the persistence of this maladaptive behavior.

https://doi.org/10.1016/j.alcohol.2026.01.060

S53

The ups and downs of BDNF signaling in the ventral hippocampus: Implications for the anxiolytic and anxiogenic actions of alcohol

Dorit Ron, Mya Gunasekaran, Ky Phamluong, Yann Ehinger

We previously discovered that the neurotrophic factor BDNF within cortico-striatal circuits functions as part of the STOP signaling pathways, which provide an endogenous brake on the escalation of alcohol drinking, seeking, and habit formation (Egervari et al., TINS 2021, Review; Gunasekaran et al., BioRxiv 2025). Here, I will present evidence suggesting that BDNF in the ventral hippocampus (vHP) also contributes to the mechanisms underlying the acute anxiolytic actions of alcohol. Specifically, we found that acute contingent and non-contingent exposure to alcohol increases the expression of specific *BDNF* exons in the CA1/CA2 and CA3 regions, but not in the dentate gyrus, of male mice, with no corresponding effects in females. We further demonstrated that this alcohol-induced increase in *BDNF* transcription requires the nuclear translocation of the scaffolding protein RACK1. Next, we examined whether acute exposure of alcohol activates the BDNF receptor TrkB. We found that TrkB is activated by alcohol in CA1/CA2 and CA3, but not in the dentate gyrus. We further showed that alcohol-induced TrkB activation stimulates ERK1/2 and CREB signaling in these same subregions. Behavioral analyses revealed that BDNF signaling is necessary for the acute anxiolytic effects of alcohol. In contrast, we observed that following repeated cycles of 20% alcohol exposure and withdrawal, as well as at the end of intermittent access to alcohol vapor, *BDNF* expression and TrkB/ERK1/2/CREB signaling were no longer upregulated in the vHP. Finally, I will present evidence that this disruption of endogenous BDNF/TrkB signaling contributes to the development of alcohol-dependent anxiogenesis.

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S54

NR2F1 is a Cross-Species Mediator of Cerebral Cortex Defects Induced by Fetal Alcohol Intoxication

S. Laguesse, M. Charlet-Briart, Van Hees L, Oskera L, Boutsen A, Bonafina A, Lavergne A, Reyskens C, Close R, Epifanova E, Helgueta S, Didone V, Tielens S. Studer M, Nguyen L

Prenatal alcohol exposure (PAE) remains the leading preventable cause of neurodevelopmental disorders, contributing to a spectrum of cognitive, sensory, and behavioral deficits collectively known as Fetal Alcohol Spectrum Disorders (FASD). To date, the precise mechanisms by which PAE disrupts brain development remain unclear, limiting the development of targeted therapies and effective prevention strategies. Alcohol is particularly harmful to the cerebral cortex, and individuals with FASD frequently exhibit impaired sensorimotor function, including deficits in tactile perception.

Using a mouse model of voluntary binge-like alcohol consumption during gestation, we demonstrate that PAE disrupts the migration and connectivity of callosal projection neurons in the developing somatosensory cortex and induces long-lasting sensory deficits. We identified NR2F1, a key transcription factor involved in neuronal migration and cortical patterning, as a novel alcohol-sensitive target mediating these effects. Mechanistically, PAE leads to upregulation of NR2F1, together with downregulation of its direct targets *Lis1* and *Kif1b*, which are essential for neuronal migration and differentiation.

Importantly, these molecular alterations are conserved in the developing cortex of human fetuses with documented prenatal alcohol exposure, as well as in human cerebral organoids engrafted into ethanol-exposed mice. Together, our findings reveal a conserved molecular and cellular pathway disrupted by PAE,

highlight NR2F1 as a key regulator in the pathogenesis of FASD, and suggest new avenues for therapeutic intervention targeting alcohol-induced neurodevelopmental impairments.

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S55

Translational Insights into Alcohol Choice Behavior: The Role of BLA-vHPC Circuitry

Olivia Colarusso, Ann Chappell, Jeff Weiner

Key diagnostic criteria for alcohol use disorder (AUD) include impaired appetitive and consummatory processes and the progressive neglect of natural rewards in favor of alcohol. Preclinical models offer a powerful platform for dissecting the neural circuits that regulate these behaviors, enabling precise manipulation of defined projections to understand their functional contributions. Emerging preclinical and clinical evidence suggest keys roles of the basolateral amygdala (BLA) and ventral hippocampus (vHPC) in the etiology of AUD. Indeed, our lab recently demonstrated that a monosynaptic excitatory BLA-vHPC projection selectively influences the regulation of seeking, but not intake, behaviors. Despite these and other important advances, few studies have considered how these important AUD-related processes are modulated when alcohol is concurrently available with an alternative reinforcer. Those that do typically lack an operant component, limiting the translational scope, as effort is nearly always required to procure alcohol. To address this critical gap, we recently developed a novel operant choice paradigm to assess alcohol self-administration in the presence of a natural reward (sucrose), while allowing for the procedural separation of seeking and intake. Notably, our recent findings indicate that operant choice is a distinct behavioral phenotype from home cage preference. These results support the assertion that operant choice may offer a more sensitive and translationally relevant model for studying AUD-related decision-making. This talk will describe the development and characterization of this novel choice paradigm and reveal how chemogenetic inhibition of the BLA-vHPC projection modulates self-administration behaviors under operant choice conditions.

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Symposium XII

Alcohol affects GABAergic fast-spiking interneurons throughout the forebrain

Chair: Max Joffe

S56

Perineuronal Net and Inhibitory Synapse Remodeling on Striatal Fast-spiking Interneurons by Alcohol

Michael S. Patton Samuel H. Sheats, Andreas B. Wulff, Paige N. McKeon, Mary H. Patton, Morgan Heckman, Allison N. Siclair, Brian N. Mathur

Alcohol use disorder is characterized by persistent drinking in the face of negative consequences. Such inflexible drinking requires dorsolateral striatum fast-spiking interneurons, which comprise roughly 1% of all striatal neurons. How chronic ethanol exposure affects fast-spiking interneuron physiology is poorly understood. We discover in mice that chronic ethanol exposure induced a dramatic loss of GABAergic, but not glutamatergic, synapses onto dorsolateral striatum fast-spiking interneuron somata and proximal dendrites where perineuronal nets, a subdivision of the extracellular matrix, are enriched. We found that chronic ethanol exposure degraded these perineuronal nets and that enzymatically degrading perineuronal nets similarly reduced GABAergic transmission onto dorsolateral striatum fast-spiking interneurons. Modeling the effect of alcohol, we find that silencing extrinsic GABAergic projections to the dorsolateral striatum increased voluntary ethanol consumption. Taken together, these data suggest chronic alcohol exposure remodels perineuronal nets and inhibitory synapses on fast-spiking interneurons to facilitate alcohol drinking.

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S57

Parvalbumin interneuron activation in prefrontal cortex reduces alcohol drinking in alcohol preferring rats

Kathleen Bryant, Baofeng Ma, Sydney Stiles, Anna Remes, Luqman Ojerinde, Christopher Lapish

Those who have a family history of alcohol use disorder (AUD) or excessive alcohol drinking are much more likely to develop an AUD than those who are family history negative. Our lab has found that increased compulsive-like drinking in P rats, a model of familial risk for excessive drinking, is associated with changes in prefrontal cortical (PFC) neural representations of behavioral control. However, the role of specific cell types play in forming these representations has yet to be investigated. The PFC contains a variety of inhibitory interneurons, including fast-spiking parvalbumin expressing interneurons (PV-INs). It is unknown whether there may be heritable differences in PV-IN function in P rats that may contribute to excessive drinking. To determine how PV-IN manipulation altered drinking behavior, a PV-IN specific Gq DREADD virus was expressed and activated in male and female Wistars and P rats during a paradigm where rats learned to associate 10% ethanol sipper access with discreet light cues. Activating PV-INs during this task reduced ethanol drinking in male P rats and aversion-resistant ethanol drinking in female P rats. These P rats were then implanted with an electrophysiological probe into PFC and neural activity was recorded. Preliminary data suggest that activating PV-INs increased cue responsiveness in both pyramidal neurons and interneurons and improved synchrony during sipper access, associated with reductions in alcohol drinking. Together, these findings demonstrate that heritable PV-IN dysfunction may contribute to AUD vulnerability, and restoring PV-IN function may serve as an exciting therapeutic target for reducing excessive drinking.

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S58

Mechanisms Driving Binge Drinking: Alcohol-Induced Alterations in PFC Basket Cell Function and mGlu5 Receptor Signaling

C. Fabian, N. Jordan, L. Nelson, M. Joffe

The prefrontal cortex (PFC) plays a critical role in regulating cognitive functions such as decision-making, motivation, and impulse control, all of which are disrupted in binge drinking. Proper PFC function depends on a delicate balance between excitation and inhibition, maintained in part by GABAergic interneurons (INs). Among these, cholecystokinin (CCK)- and parvalbumin (PV)-expressing basket cells comprise distinct classes of perisomatic-targeting interneurons that exert powerful control over cortical excitability. Previously we have shown sex-dependent adaptations to PV-INs following chronic drinking and identified a sex-specific role for the metabotropic glutamate receptor 5 (mGlu5) in regulating voluntary consumption. However, due to the broad expression of CCK in both inhibitory and excitatory cells, along with limited selective genetic tools, much less is known about the involvement of CCK-INs in binge drinking. To address this, we used CCKxVGAT-Cre mice to selectively target inhibitory CCK cells and employed the Drinking in the Dark (DID) model of binge alcohol exposure. After four weeks of DID, we performed whole-cell recordings from fluorescently labeled PV- and CCK-INs in prelimbic PFC. Binge drinking produced adaptations in intrinsic properties, synaptic strength, and mGlu5 receptor signaling across both cell-types. Additionally, chemogenetic activation of PFC PV interneurons during operant self-administration reduced ethanol responding in both sexes. Finally, we used in vivo fiber photometry during operant drinking to assess PFC basket cell activity in alcohol reinforcement. Together, these findings show that binge drinking differentially affects PFC PV- and CCK-INs and underscore the potential involvement of PFC basket cells in drinking behaviors.

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S59

Alcohol modulation of BLA network states involved in emotional processing

Katrina Blandino, Alyssa DiLeo, Jamie Maguire

The cycle of addiction, as it relates to alcohol use disorder (AUD), involves three

interconnected stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. The binge/intoxication stage is thought to be driven by the anxiolytic effects of alcohol; whereas, anxiogenic effects following chronic alcohol exposure contribute to the negative affective states associated with withdrawal, termed "hyperkatifeia". Thus, understanding how alcohol impacts anxiety states is highly relevant to AUD. Our work demonstrates a novel mechanism contributing to the impact of alcohol on anxiety states which involves the modulation of basolateral amygdala (BLA) network states, which have been shown to govern valence and emotional processing. BLA network states are orchestrated by parvalbumin-positive (PV) interneurons, which may contribute to the role that these interneurons play in mediating the effects of alcohol on anxiety states. Recent work from our laboratory demonstrated that alcohol is capable of modulating oscillatory states in the BLA, which we propose contributes to the anxiolytic effects of acute alcohol exposure. Further, we demonstrate that chronic ethanol exposure perturbs BLA network states, which we propose contributes to withdrawal-associated behaviors. Interestingly, our work also demonstrates that the extent to which alcohol modulates oscillations in the BLA correlates with the amount of future alcohol consumption. These data support a novel mechanism, involving modulation of BLA network states, in contributing to the impact of alcohol on anxiety states, thereby, contributing to the cycle of AUD.

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Symposium XIII
Alcohol Effects: Recent developments on neuroimmune mechanisms and brain networks.
Chairs: Marina Guizetti and Robert Messing
Discussant: Laura Ferguson

S60
Toll-like receptor 3 signaling in neurons regulates responses to ethanol through interferon and non-interferon dependent mechanisms

R.O. Messing, Y.A. Blednov, G.A. Dilly, C. Fleischer, J.D. Plotkin

We previously found that knockout of TLR3 in neurons of the dorsal striatum reduces alcohol consumption and acute functional tolerance to alcohol in male mice. The major downstream effector of TLR3 signaling is interferon beta. We performed studies testing the hypothesis TLR3-mediated generation of interferon in the dorsal striatum regulates alcohol consumption in male mice. We found that knockout of the TLR3 adapter protein TRIF (TIR-domain-containing adapter-inducing interferon-β) in the dorsal striatum phenocopied TLR3 knockout phenotypes of reduced alcohol consumption and tolerance. Systemic treatment with the TBK/IKKepsilon inhibitor amlexanox also decreased ethanol consumption and reversed effects of the TLR3 agonist poly I:C on acute responses to alcohol.
Systemic administration of interferon-β primed animals for high levels of subsequent ethanol consumption whereas knockout of type 1 interferon receptors in striatal neurons delayed escalation of ethanol intake. However, knockout of type 1 interferon receptors did not alter acute behavioral responses to alcohol. These findings suggest that TLR3 stimulates interferon production in striatal neurons which in turn promotes escalation of ethanol consumption via autocrine stimulation of type 1 interferon receptors in striatal neurons. In contrast, effects of TLR3 signaling on sustained drinking, ethanol intoxication and tolerance appear to involve additional mechanisms activated by TLR3, TRIF, and TBK/IKKepsilon. These non-interferon mechanisms likely involve GABA-A receptors since acute responses to diazepam were increased in TLR3 and TRIF striatal knockout mice but not in interferon receptor knockout mice.

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S61
Sex-dependent reorganization of functional and structural brain networks in Alcohol Use Disorder: The Triple Network theory perspective

Pilar Ortiz Teba, Marion Sourty, Marion Rame, Leatitia Degiorgis, Laura-Adela Harsan

Alcohol Use Disorder (AUD) induces extensive brain alterations, yet the specific neuroadaptations driven by chronic alcohol exposure remain poorly characterized. We hypothesized that prolonged alcohol consumption reorganizes functional and structural brain networks in a phenotype- and sex-dependent manner. Using a murine every other day two-bottle choice paradigm, we characterized alcohol consumption patterns by quantifying drinking dynamics, mean intake, alcohol preference, and cumulative intake. These behavioural measures were integrated with multimodal neuroimaging approaches: resting-state fMRI to assess functional connectivity (FC) and diffusion tensor imaging with fiber tractography to evaluate structural connectivity (SC). Network graph theory metrics were computed to characterize topological profiles across experimental groups.
Our findings delineate distinct sex-specific neuroadaptations: alcohol-exposed males exhibit increased network integration across both functional and structural modalities, whereas females engage enhanced network segregation as a dominant adaptive strategy.
To elucidate the network-specific functional implications of these reorganizational trajectories, we applied graph theory topology analyses to the Triple Network framework -Default Mode (DMN), Salience (SN), and Lateral cortical (LCN) networks. Sex-stratified correlations linked triple network topology indices with behavioural variables across both connectivity modalities. Node-level analyses highlighted key regions driving network reconfiguration and their behavioural correlates, underscoring sex-specific alterations in Triple Network interactions following alcohol exposure.
Finally, Partial Least Square integrative model delineated the multivariate relationships between Triple Network components and alcohol-related behavioural phenotypes, identifying candidate neurocircuitry-based biomarkers for AUD progression.

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S62
Glial cell diversity and molecular landscape of alcohol use disorder and animal models

N. Salem, M.M. Friske, A.S. Warden, R. Barchiesi, A.J. Roberts, M. Roberto, R.D. Mayfield

Single cell and spatial transcriptome technologies have shown that brain glial cells are particularly sensitive to the effects of alcohol in both human and animal studies. We utilized single nucleus RNA sequencing (snRNA-seq) and Xenium In Situ spatial profiling to examine the dorsolateral prefrontal cortex from AUD and matched control cases, and medial prefrontal cortex from C57Bl6/J mice exposed to a chronic intermittent ethanol (CIE) paradigm. In both human and mouse, glial cells including oligodendrocytes, astrocytes, and microglia were the most sensitive to alcohol and were enriched with alcohol responsive genes. Integration anchors were selected followed by the harmonization of the two datasets. Unsupervised clustering was performed to identify mouse and human specific cell clusters. We identified a cluster of microglial cells that was specific only to human AUD. This cluster of microglia cells was enriched in inflammatory border-associated macrophage (BAM) markers such as TIMP2 and PTPRC, disease-associated microglia (DAM) markers including CLEC7A and MRC1, as well as genes associated with cytokine signaling including TLR2 and IL1B. In contrast, human and mouse overlapping microglia clusters were enriched with genes associated with homeostatic functions (e.g. P2RY12, CX3CR1, and CST3). Glial cells also harbored DEGs implicating blood brain-barrier (BBB) disruption across species and animal models. In human AUD, there was strong IFN and IL-15 signaling in microglial expression patterns associated BBB function. Our data suggests alcohol and chronic neuroimmune activation dysregulates specific gene expression patterns in glial cells and induces long-term BBB dysfunction in both a cell type-specific manner. These changes may underlie the observed escalated alcohol consumption.

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S63
The Role of Microglia in Chronic Alcohol and Withdrawal

J.D. Wherry, M.R. Ross, D.V. Gil, G.E. Homanics, S.P. Farris

Alcohol Use Disorder (AUD) is a serious psychiatric disorder affection millions of individuals. Human and animal studies have suggested multiple potential molecular mechanisms involved in AUD; however, may of the underlying systems involved in the etiology of AUD are unknown. Microglia are the resident neuroimmune cells in the central nervous system, which are hypothesized to be involved in regulation of alcohol consumption and other alcohol-related

behaviors (*e.g.,* pain). Using an established mouse model of chronic intermittent ethanol vapor (CIEV) exposure in male and female C57BL/6J mice we assessed functional changes in microglia following chronic ethanol exposure and withdrawal. CIEV produced persistent mechanical evoked hypersensitivity in both male and female mice. Additionally, B6J mice showed a significant increase in facial grimace behavior during CIEV withdrawal and following a peripheral immune challenge with lipopolysaccharide (LPS). CIEV and LPS both showed statistically significant decreases in multiple indices of microglia morphology. Morphological changes were directly correlated with mean grimace scores, suggesting a critical role of microglia activation for spontaneous affective pain-related behavior. To identify potential neuroimmune mechanisms we conducted RNA-Seq analysis of chronic ethanol exposed microglia. Ethanol caused a significant increase in genes known to be involved in transcriptional regulation and neuroimmune activation (Fos, Aif1, Tnf), as well as changes in other protein-coding and non-coding genes and pathways. Overall, our research provides new mechanistic insights into ethanol-induced alterations of microglia and potentially contributes to the rationale design of novel pharmacotherapies for AUD.

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Symposium XIV
Alcohol and the Heart: Basic Science to Clinical Outcomes Affecting Stress, Craving and Excessive Alcohol Intake
Chairs: Rajita Sinha and David Eddie

S64
A Randomized Clinical Trial of Heart Rate Variability Biofeedback for Alcohol and Other Drugs Use Disorders

David Eddie, Marina Nguyen, Katherine Zeng, Sara Mei, Noah Emery

Preliminary evidence suggests heart rate variability biofeedback (HRVB) can reduce craving and negative affect in alcohol and other drug (AOD) use disorders, yet effects on substance use and the utility of newer wearable HRVB devices have been under-tested. We conducted a phase II randomized clinical trial to evaluate second-generation, wearable HRVB on negative affect, positive affect, craving, and AOD use among adults with AOD use disorders. Participants received 8 weeks of outpatient treatment and were recruited virtually across the United States (February 2023–June 2024). Of 260 screened, 120 treatment-seeking adults were randomized to HRVB + treatment as usual (TAU) or TAU alone. Primary outcomes were assessed via ecological momentary assessment. The sample was 60% female; mean (SD) age was 46.18 (11.59) years. Compared with TAU, HRVB produced significant reductions in negative affect and craving over 8 weeks, whereas controls showed increases; groups did not differ on positive affect. HRVB also yielded a significantly lower proportion of AOD-use days, corresponding to a 64% reduction relative to controls. Treatment condition moderated the within-person association between craving and subsequent AOD use; participants receiving HRVB were less likely to use following elevations in craving. Findings indicate that second-generation, wearable HRVB can reduce negative affect, craving, and substance use in early recovery from AOD use disorders, potentially by weakening the craving-to-use pathway. These results support HRVB as a promising adjunct to standard care and warrant confirmation in phase III trials.

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S65
Cardiac Interoception: A Window into Physiological Changes in Alcohol Use Disorder

Mateo Leganes-Fonteneau

Cardiac interoception provides a perceptual channel for monitoring internal physiological changes and offers a crucial dimension for understanding how bodily states shape cognition, affect, and behavior. Because cardiac dynamics are directly implicated in the etiology of addiction, studying cardiac interoception allows us to probe mechanisms through which internal signals contribute to subjective experience and maladaptive patterns of use. My work addresses this gap by linking acute alcohol effects on interoception with the conscious experience of intoxication.
In a series of studies, I show that alcohol acutely modulates cardiac interoception and that these changes are associated with subjective alcohol effects and expectancies in heavy drinkers. This suggests that interoceptive processes provide a substrate through which alcohol influences conscious awareness, thereby shaping the phenomenology of intoxication. At the same time, interoceptive sensitivity can reflect adaptive versus maladaptive detection of bodily states, underlining its potential clinical relevance for addiction.
A second line of research examines resonance breathing, a biofeedback technique that modulates cardiac dynamics to generate healthful benefits. Experimentally, I found that resonance breathing effects on bodily states feed into improved cardiac interoception, pointing to a mechanism by which its therapeutic benefits may emerge. Enhanced bodily awareness could help individuals respond more adaptively to craving episodes or regulate emotions more effectively.
Together, these studies identify cardiac interoception as a key process linking physiology to conscious experience in addiction. They also open pathways for extending interoceptive research beyond cardiac signals, with the goal of generating clinically meaningful insights and innovative interventions.

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S66
Integrated Cardio-behavioral Responses Define Emotional States

Jérémy Signoret-Genest, Schukraft Nina, César Redondo Alañon, Sara Lourenco dos Reis, Philip Tovote

While behaviour is the most common readout for inferring affective states in animals, emotional reactions are inherently multi-modal, including autonomic adaptations such as heart rate variations. Conceptual models like the threat imminence framework account for defensive behavioural diversity, yet their translation to observational studies remains difficult: identical behaviours may reflect different internal states, and associated autonomic responses have often appeared contradictory. This highlights the need for more fine-grained characterization to uncover underlying neuronal mechanisms.
Using electrocardiogram recordings in freely moving mice, we combined cardiac and behavioural data to identify reproducible cardio-behavioural signatures of defensive states. This revealed short-lived "microstates" (stereotypical associations at the level of single behaviours) as well as latent "macrostates" (longer-lasting, hidden influences such as threat context). These macrostates cannot be inferred from behaviour or heart rate alone, yet capture higher-order internal states. Building on this, we established causal links between defensive microstates and neuronal populations in the ventrolateral periaqueductal gray, and more recently extended the framework to prefrontal cortex activity to better understand interactions between the environment, behaviour, and autonomic responses.
By integrating behaviour and heart rate across timescales, this approach provides a dynamic, mechanistic lens on the organization of emotional and homeodynamic states.

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S67
Particular Anterior Insula outputs may mediate specific arousal regulation mechanisms during alcohol drinking and anxiety

Thatiane De Oliveira Sergio, Raizel M. Frasier, Sarah E. Wean, Phillip A. Starski, Alecsander Zareb, Angela Grippo, Frederic W. Hopf

Anterior Insula (AIC) likely mediates important aspects of alcohol drinking and anxiety, but the importance of specific AIC outputs remains incompletely understood. We combined heartrate telemetry and, in separate long-drinking male and female Wistar rats, wireless optogenetic inhibition of AIC outputs to posterior insula (AIC-PIC) or nucleus accumbens (AIC-NAc). By better understanding AIC arousal regulation related to drinking and anxiety, we hoped to uncover novel treatment biomarkers. Overall, males utilized AIC-PIC for engagement with anxiety, related to parasympathetic promotion of behavior, while females had more complex utilization of AIC-NAc-related sympathetic states, along with AIC-PIC. Indeed, AIC-NAc could promote or inhibit different aspects of female anxiety responding. We compared novelty suppression of feeding (NSF), where food-restricted rats undergo conflict between food and bright light, and Light-Dark Box (LDB), which pits light/novelty against drive to explore. Inhibiting AIC-PIC but not AIC-NAc reduced male engagement with anxiety more broadly. In females inhibiting female AIC-NAc strongly increased NSF time near food/light, perhaps removing AIC-NAc-mediated caution. In LDB, AIC-PIC and AIC-NAc together sustained females' initial time in the light,

perhaps reflecting taking the time for sufficient assessment, And also persistent engagement despite greater arousal. Indeed, males used AIC-NAC + AIC-PIC for compulsive drinking, while females used only AIC-PIC for compulsion, perhaps better attentional control and thus easier engagement. Finally, greater composite anxiety behavior related to greater compulsive intake in females, but not males, consistent with females more often choosing higher-arousal-regulation strategies. Together, we provide new evidence for differential AIC-PIC and AIC-NAc deployment across sexes and task requirements.

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Symposium XV
Impact of Alcohol Exposure on Development of Emotional Regulation and Related Behaviors Across the Lifespan
Chairs: Jennifer Thomas and Rosana Camarini

S68
Evaluation of Early Prenatal Ethanol Exposure on Stress/Anxiety-Related Phenotypes

Kristin Hamre, Emma Norman, Pranav Rajashekar

Prenatal exposure to ethanol can cause alterations in stress/anxiety phenotypes. Moreover, both stress responses, and the type and degree of ethanol's teratogenic action are influenced by genetics.
Previously, we evaluated ethanol-induced cell death in the telencephalon in the neural tube in a genetic reference population, BXD recombinant inbred mice. We find variations in cell death among strains following a single binge exposure on embryonic day 9. In the current study, we selected strains with low, moderate or high telencephalonic cell death and examined cell loss in the diencephalon, an area critical to the stress response. The results were consistent between the telencephalon and diencephalon: similar relative levels of cell death were observed in both regions. To further examine the functional consequences of early ethanol exposure, a separate cohort of mice were allowed to mature to adulthood and tested on behavioral battery that included tests of learning and memory (T-maze and Y-maze) and anxiety-related phenotypes (elevated plus maze and open field). While there were no differences between ethanol and control groups in the elevated plus maze, the ethanol-exposed mice showed alterations in habituation and in the time in the center in the open field, consistent with an alteration in anxiety-like behavior. These results suggest that a single binge-like ethanol exposure early in gestation can alter anxiety-like responses and suggest that further testing is warranted to parse out the role of early ethanol exposure on stress responsivity and anxiety-like phenotypes.

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S69
The impact of timing of developmental alcohol exposure on stress-associated neurobehavioral outcomes

David Linsenbardt, Mitchell Morningstar, Abbey Myrick, Monserrat Orozco, Dominic Furlano, Seth David, Hannah Aranda, Aiden Hargis, Fernando Valenzuela

Alcohol is a known teratogen, but it affects fetal development in a variety of complex ways that depend greatly on the timing and pattern of exposure. To develop a better understanding of how different types of exposures lead to different stress-associated neurobehavioral outcomes, we exposed mice to alcohol at different stages of development, and then tested them on a variety of behavioral assays. We found that exposure to alcohol during the time period equivalent to the 1st and 2nd trimester in humans resulted in increased anxiety-like behavior in females, a developmental (weight) delay in males, and increased risk-taking. In mice exposed to alcohol during the time period equivalent to the 3rd trimester in humans, we observed impaired fear conditioning and robust home cage hyperactivity when housed in social isolation. We then labeled neural networks active during risk-taking and fear conditioning to identify neural circuits mediating the observed behavioral differences. We found that 1st-2nd trimester alcohol exposure engaged an almost identical circuit as controls during risk-taking, with one exception – the Dorsal Cortex of the Inferior Colliculus (DCIC) was robustly activated in alcohol subjects only. In 3rd trimester alcohol exposed subjects, we found profound alterations in the 'Papez' learning and memory circuit, including decreased activity of the anteroventral (AV) and anterodorsal (AD) thalamus, broad hyperconnectivity in males, and functional connectivity differences to the basomedial amygdalar nucleus. These results together identify alcohol-induced developmental period-specific alterations in brain and behavior, and pave the way for functional/molecular studies designed to reveal novel treatment targets.

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S70
Some depressing thoughts on how ethanol might affect synaptic communication

Brian Christie

Long-term depression (LTD) in the dentate gyrus (DG) is a cellular mechanism to reduce synaptic strength and is associated with stress and depression. We and others have shown that chronic stress can decrease DG function, alter plasticity, and reduce adult neurogenesis, contributing to impaired learning, memory, and mood regulation. Acute stress impairs memory retrieval and facilitates the induction of long-term depression (LTD) in the hippocampus. These effects involve the GluN2B receptor, suggesting that prenatal exposure might alter the role of these receptors. Prenatal ethanol exposure (PNEE), in contrast, impairs the capacity for LTD in the hippocampus, while producing impaired learning and memory performance like that seen with acute stress. Ethanol is a non-competitive inhibitor of NMDA receptors, so we next directly applied Ethanol (50 or 100 mM) and examined the effects on LTD. Only 50 mM EtOH reliably inhibited LTD, and this inhibited NMDA currents in animals 28 days and older. Increasing EtOH to 100 mM could impair NMDA currents in all age groups. When we examined animals younger than 28 days, we found that CB1 receptors played a larger role in LTD induction than NMDA receptors. Interestingly, CB1 receptor antagonists can increase anxiety-like behaviours and worsen stress responses, suggesting that PNEE may impact the role of CB1 receptors and NMDA receptors in LTD. These results imply that functional changes in hippocampal synaptic plasticity associated with stress may involve overlapping and convergent pathways.

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S71
Insular parvalbumin interneurons as modulators of impulsivity and ethanol-seeking behavior in adolescent mice

F.R. Bezerra, G.J.F. Damaceno, A. Anjos-Santos, C.A. Favoretto, B.T. Rodolpho, P. Palombo, V. Vialou, K.P. Abrahao, F.C. Cruz

Ethanol is the most widely consumed substance of abuse worldwide and is linked to high morbidity and mortality rates. Adolescents exhibit higher impulsivity, a key risk factor for ethanol use. Given the insular cortex's crucial role in impulsivity regulation, potentially modulated by parvalbumin (PV) GABAergic interneurons, we hypothesized that changes in PV interneuron activity may contribute to ethanol consumption in adulthood. To investigate this, we assessed impulsivity-like behavior and ethanol intake in male adolescent (Postnatal Day – PND 28) and adult (PND 64) C57BL/6 mice using the Omission-Contingency Learning (OCL) test and the two-bottle choice paradigm. Adolescent mice exhibited higher impulsivity and ethanol consumption than adults. Double immunofluorescence labeling (Fos/NeuN and Fos/Parvalbumin) revealed that reduced activation of PV interneurons was associated with increased impulsivity, higher ethanol consumption, and preference. To test causality, we used chemogenetic modulation of PV interneurons in transgenic PV-Cre mice. Interneurons' chemogenetic activation reduced both impulsivity and ethanol-drinking behavior. In conclusion, diminished PV activity in the insular cortex of adolescent mice seems to be linked to increased impulsivity and alcohol-seeking behavior.

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Symposium XVI
Role of Specific Amygdala & Cortical Cell Populations in Excessive Alcohol Drinking
Chair: Nicholas Gilpin

S72
Old dogs and new tricks in the search for treatments to reduce escalated alcohol drinking after stress

Nick Gilpin, Jason Middleton, Marcus Weera, Jungyup Suh, Maria Secci, Rajani Maiya

Post-Traumatic Stress Disorder (PTSD) affects approximately 7.7 million Americans and is highly comorbid with Alcohol Use Disorder (AUD). The lifetime prevalence of PTSD is about 8% in the U.S population and even higher among combat veterans. Individuals with PTSD are more likely to develop AUD, with 22-43% of those with PTSD meeting the criteria for AUD. This comorbidity results in substantial health and financial burdens, making it critical to understand the biological basis of excessive alcohol consumption in individuals with PTSD. Our work aims to uncover the neurobiological mechanisms underlying this comorbidity by studying the role of specific neurons and molecules involved in alcohol-related outcomes following traumatic stress. Specifically, we have spent years investigating the role of corticotropin-releasing factor type-1 receptor (CRF1) signaling and CRF1 + cells in the central amygdala (CeA) for their roles in escalated alcohol drinking after traumatic stress. Currently, we are extending this work by transcriptionally profiling CRF1 + cells in the CeA using single-nucleus RNA sequencing (snRNAseq). Our data indicate enrichment of specific molecules in CeA CRF1 + cells, as well as stress-induced changes in the expression of specific genes in CeA CRF1 + cells. We have been working to validate our snRNAseq findings at the mRNA, protein, and functional levels with molecular biology, slice electrophysiology, and behavioral pharmacology approaches. This work builds on decades of scientific data showing that CRF1 is a powerful regulator of excessive alcohol drinking, and takes a new tact to identify translational targets for development of effective treatments in patients with AUD and/or PTSD.

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S73

Single nucleus RNA sequencing identifies Fgf-R1 signaling in central amygdala as a neural substrate of punishment-resistant alcohol self-administration

Markus Heilig, Estelle Barbier, Leon Höglund, Li Xu, Robert O. Messing, Dayne Mayfield

Using punishment-resistant alcohol self-administration in rats as a model of compulsivity, we identified PKCdelta + neurons in centrolateral amygdala (CeL) as a neural substrate of this behavior.
Here, we searched for the underlying molecular mechanisms. Male and female rats were characterized for compulsivity, then brains were processed for snRNAseq in the CeA (n=12/group/sex). Weighted Gene Co-Expression Network Analysis (WGCNA), applied to GABAergic cells identified modules with differential expression in compulsive versus non-compulsive as well as compulsive versus yoked controls. PKCdelta:cre rats, and a Cre-dependent shRNA AAV5 vector were used for cell-type specific knockdown (KD). Initial analyses focused on males. The top differentially expressed module mapped to PKCdelta neurons. Fgf-R1 had the highest loading on the module eigengene. RNAscope confirmed Fgf-R1 overexpresson in CeL of compulsive rats, and selectively in PKCdelta neurons. Compulsive PKCdelta:cre rats received CeL injections of Cre-dependent Fgf-R1 KD (n=7) or a control vector (n=8). Compulsive self-administration rates were suppressed in the KD vector group. Up-regulated Fgf-R1 expression in PKCdelta + CeL neurons is a causal factor behind compulsive alcohol self-administration. The FDA approved Fgf-R1 inhibitor inigratinib is brain penetrant, and we intend to use this drug to determine whether our findings in rats can be translated into humans.

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S74

Sex differences of insular cortex function in persistent alcohol drinking in mice

Claudia Fornari, Carmen Guerrero-Márquez, Praneeth Namburi, Yoni Couderc, Camille Penet, Céline Nicolas, Anna Beyeler

Among indicators of AUD vulnerability, binge drinking has been identified as one of the strongest risk factor. Sex differences in both AUD and binge drinking have been found in clinical and preclinical studies. At the neurobiological level, the insular cortex plays an important role in AUD, with the anterior (aIC) and posterior (pIC) divisions supporting different functions. However, the contributions of the aIC and pIC in sexual dimorphism of alcohol binge drinking and the persistence of alcohol drinking despite aversion remained to be uncovered. Using the drinking in the dark model in mice, we validated that female mice have a higher binge ethanol intake compared to males. To evaluate persistent ethanol consumption despite aversion, we supplemented ethanol with the bitter compound quinine, and found a higher persistent drinking in females compared to males. Using fiber photometry recordings, we revealed that both aIC and pIC glutamatergic neuron activity increased during binge and persistent ethanol consumption. The amplitude of response was independent of sex in the aIC for both binge and persistent drinking, as well as in the pIC although only for binge drinking. Interestingly, pIC activity was specifically higher in female, compared to male mice during persistent drinking. Consistently, chemogenetic inhibition of pIC glutamatergic neurons selectively reduces persistent ethanol drinking in females, while selectively decreasing quinine consumption only in males.

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S75

Chronic Alcohol Reshapes Serotonin-Dynorphin Dynamics in the Nucleus Accumbens to Inhibit Social Reward

Catherine A. Marcinkiewcz

Drugs that enhance serotonin (5-HT) transmission in the brain are used to treat co-morbid anxiety and depression in individuals with alcohol use disorder (AUD), but emerging evidence suggests that serotonin may worsen negative outcomes associated with alcohol abstinence. The goal of the present study was to elucidate the neural circuits underlying affective disturbances after chronic intermittent ethanol (CIE) in a mouse model. Our results indicate that CIE induced social deficits in male, but not female, mice. 5-HT hyperexcitability was also limited to males. Using iDISCO, we found that chemogenetic activation of DRN 5-HT neurons enhanced c-Fos in the nucleus accumbens (NAcc) of ethanol-naïve mice, while CIE increased 5-HT transients in the NAcc during social interaction, suggesting that excessive 5-HT signaling in the NAcc may drive CIE-induced social deficits in males. This was confirmed using chemogenetic manipulation of the 5-HT DRN–>NAcc pathway, which modulates social behavior in male CIE-exposed mice. We then demonstrated that 5-HT2c receptor-expressing dynorphin neurons in the NAcc mediate this process. Specifically, pro-dynorphin and 5-HT2c mRNA expression were upregulated in the NAcc of CIE mice and humans with AUD, and there is a 5-HT2c-dependent increase in dynorphin neuronal excitability in the NAcc after CIE. Furthermore, genetic knockdown of pro-dynorphin or 5-HT2c receptors in dynorphin neurons rescued social deficits after CIE. Chemogenetic activation of NAcc dynorphin neurons also inhibited local dopamine release during social interaction. Together, these results indicate that CIE reduces social behavior by inhibiting dopamine release via a 5-HT2c-dynorphin circuit in the NAcc.

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Symposium XVII
Alcohol and stress impacts on cortical limbic regulation of cognitive-behavioral processes
Chair: Kathleen Grant
Discussant: Verginia Cuzon-Carlson

S76

Remembering to drink: Biases in forming alcohol-related episodic memories among risky drinkers

Elizabeth Goldfarb

Remembering past experiences with alcohol is a powerful driver of future drinking. Although drinking is often thought to impair episodic memory, we have shown that memory for alcohol-related contexts is stronger in alcohol use disorder (AUD), can be augmented with hydrocortisone at encoding, and can predict later drinking. However, it is unclear how risky (non-AUD) drinkers form memories for alcohol-related contexts, and whether context memories can also drive later binge drinking. We recruited demographically-matched light (N = 35) and risky (regular binge; N = 35) drinkers to complete an associative learning task during an fMRI scan. During this task, they encoded alcohol/scene and object/scene pairs and rated their emotional responses to each. The next day, participants retrieved affective and context memories for these pairs, followed by 2 weeks of smartphone-monitored drinking behavior. We found that risky drinkers had stronger emotional responses to alcohol/scene pairs, rating them as inducing more arousal (group x stimulus: $p = .009$) and craving (group x stimulus: $p = .02$), and remembering these emotional responses more vividly the

next day (group x stimulus: p = .006). Consistent with our previous findings, memory for alcohol contexts predicted later drinking, with stronger memory predicting more drinking days (p = .02), particularly binge drinking days (p = .004). Preliminary neuroimaging analyses indicate that, as in our study with hydrocortisone, hippocampal circuitry prioritizes alcohol context memory. Ongoing analyses are testing the relationships between endogenous cortisol, memory, and drinking.

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S77

Impact of alcohol and stress on norepinephrine, frontal cortex dependent behaviors

Katy Nippert

Alcohol use disorder (AUD) is characterized by persistent inflexible alcohol-seeking despite associated negative outcomes. Behavioral inflexibility in AUD extends to other tractable behaviors, including cognition. Cognitive flexibility is dependent on dorsomedial frontal cortex (dmFC) function. The current study investigated whether changes in noradrenergic signaling in dmFC contribute to this behavioral shift toward inflexibility after chronic alcohol and stress.
Adult male and female C57BL/6J mice were trained on intermittent access drinking (15% EtoH) and a novel operant attentional set shifting task (ASST). Once behavior and drinking stabilized, mice were exposed to chronic intermittent ethanol vapor and forced swim stress (CIE/FSS), or air exposure and no stress for control (AIR/NS). Post-alcohol and stress ASST sessions occurred following two and four cycles of CIE/FSS or AIR/NS. We used Bayesian analysis to extract response patterns in ASST. Following the final ASST, brains were flash frozen for *in situ* hybridization assessing noradrenergic receptor transcripts in dmFC.
CIE/FSS mice were less likely to complete extradimensional shifts (EDS) during ASST after CIE/FSS, and those that did EDS required more trials to reach criterion, compared to controls or their baseline. Bayesian analysis revealed that CIE/FSS animals increased spatial perseveration responses at the expense of task performance. In contrast, AIR/NS animals exhibited more exploration in Bayesian response strategies. These results demonstrate how CIE/FSS may act as a driver of impaired flexibility, through the adoption and perseveration of suboptimal strategy usage, due to underlying changes in noradrenergic receptors in dmFC.

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S78

Sex-Dependent Neuropil Propagation Shapes Recurrent Dynamics in Primate Prefrontal Cortex

Suzanne Nolan

This talk will detail our recent work using ex vivo high-density calcium imaging to interrogate dorsolateral prefrontal microcircuits in rhesus macaques following alcohol self-administration and attentional set-shifting. We demonstrate sexually dimorphic mechanisms of recurrent activity whereby females display lower thresholds for input-triggered propagation of recurrent events as well as non-linear scaling of input-output relationships. Further, recurrent activity was mediated by similar ensemble recruitment patterns between the sexes, while striking differences in excitability of non-somatic compartments accounted for the differential population level signals in females. These findings reveal dimorphic mechanisms for generation of cortical representations that support similar behavioral repertoires, suggesting distinct circuit motifs can support cognitive flexibility. We also consider how the experience of stress may differentially modulate circuit-level mechanisms that support cognitive flexibility across sexes.

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S79

Kappa Opioid Receptors on dopamine terminals drive anxiety-like behavior and hypodopaminergia in response to stress and alcohol exposure in mice

Katherine Holleran

This talk will describe our recent findings on the impact of kappa opioid receptor (KOR)-mediated inhibition of dopamine signaling on behavior following exposure to stress and chronic alcohol using projection-specific knockdown strategies and the dopamine fluorescent photosensor dLight in the nucleus accumbens and basolateral amygdala. Our laboratory has consistently demonstrated across species (from mouse to rat to nonhuman primate) that stress or chronic alcohol robustly augments the ability of KOR agonists to inhibit dopamine release in the nucleus accumbens. The present talk will discuss findings using a targeted projection-specific viral knockdown of KORs to demonstrate a causal role of these receptors within dopamine terminals in the nucleus accumbens in driving anxiety-like behavior, as well as explore the role of dopamine terminal KORs in hypodopaminergia driven by stress and chronic alcohol exposure via *ex vivo* fast scan cyclic voltammetry. We find that both stress and alcohol drive hypodopaminergia, possibly though divergent mechanisms involving the KOR. Further, this talk will highlight our recent findings using the dopamine fluorescent photosensor dLight in conjunction with KOR pharmacology to elucidate impacts on both spontaneously-arising and alcohol drinking-associated dopamine signaling within dopamine terminals in the nucleus accumbens and the basolateral amygdala in awake and behaving mice. We will also consider how differential dopamine signaling in the nucleus accumbens vs the basolateral amygdala may confer differential salience and/or temporal encoding of stimuli as well as how chronic alcohol or stress could impact these kinetics.

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Symposium XVIII
Individual differences in alcohol response and related outcomes: Behavioral and neurobiological mechanisms across species
Chair: Marcus Weera

S80

Neural epigenomic and transcriptomic landscape underlies individual variability in risk for AUD

Kip Zimmerman, Alex Bustabad, Clara Lowe, Dongqin Zhu, Frances Miller, Rita Cervera-Juanes

The heterogeneity of alcohol use disorder (AUD) disorder in etiology, progression, and severity of symptoms complicate its treatment. Thus, understanding each individual's biological makeup is paramount to identify and design the most effective treatment in a personalized manner. We use multiomics analyses of the dorsolateral prefrontal cortex and nucleus accumbens of non-human primates before and after chronic ethanol use to identify pre-existing individual molecular variability in risk as well as in severity to AUD. We have identified epigenetic signatures in the alcohol-naïve macaque brain that demonstrates, that in some individuals, the glutamatergic system is wired to increase risk for heavy ethanol intake. We have generated data indicating that these epigenetic signals might be contributing to the neural splicing landscape, which will drive synaptic plasticity, function, and ultimately, behavior. Furthermore, and following chronic ethanol use, manipulation of a subset of these genes results in individual variability in response to treatment to reduce excessive ethanol use. Specifically, our data demonstrates that only a subset of individuals respond to an agonist of a novel GPCR gene identified in our study. In all, our data demonstrates an underlying epigenetic signature, and associated splicing landscape, that drives risk or resilience to excessive ethanol use and response to treatment.

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S81

Discrepancy-based resilience is associated with individual differences in problematic alcohol use and stress-related psychological and physical comorbidities

Melanie Schwandt, Vijay Ramchamdani, Nancy Diazgranados, David Goldman

Resilience, or the successful adaptation to stressful life experiences, is a multidimensional construct that has been linked to psychosocial and physical health outcomes including alcohol use disorder (AUD). Discrepancy-based psychological resilience (DBPR) is an individualized measure of resilience operationalized as the difference between an individual's actual and expected level of psychological functioning as a function of stress load. DBPR has been examined in trauma-exposed populations and twin samples and has been found to be moderately heritable. We examined DBPR in a clinical sample that represents the full range of alcohol use and misuse. Participants (n=1315) were enrolled in

the NIAAA Natural History Protocol and included non-drinkers, moderate drinkers, heavy drinkers, and those seeking treatment for AUD. Latent factors of psychological distress and stress exposure were utilized to calculate individual DBPR scores. We found that DBPR was negatively associated with problematic alcohol use, severity of AUD, and the number of comorbid substance use and psychiatric disorders. In addition, DBPR was positively associated with overall physical health, and negatively associated with heart rate, self-reported pain, and systemic inflammation. Analysis of several resilience-related polygenic risk scores (PRS) revealed that PRS for both problematic alcohol use and neuroticism were negatively associated with DBPR, although the effect sizes were small. Our findings add to existing research on individual resilience, which is known to be influenced by psychological, biological, and environmental factors. Interdisciplinary approaches aimed at building resilience could potentially improve recovery outcomes in those seeking treatment for AUD.

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S82

Blunted lateral hypothalamus–lateral habenula circuit responses underlie reduced alcohol aversion in stress-susceptible 'Avoider' rats

Olivia R. Brunke, Sydney M. Bonauto, Nicholas W. Gilpin, Marcus M. Weera

Post-traumatic stress disorder (PTSD) is frequently comorbid with alcohol use disorder (AUD) and marked by persistent avoidance of trauma-associated cues. In a rat model, a single episode of predator-odor stress produces enduring avoidance in a subset of "Avoider" rats, paralleling individual differences in human stress reactivity. We previously showed that Avoiders escalate their alcohol self-administration and exhibit prolonged anxiety-like behavior after stress. Here, we tested whether Avoiders are also less sensitive to alcohol's aversive properties, a factor that may contribute to their heightened drinking. Using place- and taste-conditioning paradigms, we found that stressed Avoider rats were more resistant than Non-Avoiders to developing conditioned aversion to alcohol (1.5 g/kg), indicating blunted sensitivity to its aversive effects. c-Fos immunohistochemistry revealed group differences in the lateral habenula (LHb): alcohol robustly increased LHb c-Fos in Non-Avoiders and unstressed controls but decreased it in Avoiders. In the lateral hypothalamus (LH), alcohol reduced c-Fos expression only in Avoiders. Alcohol did not produce group differences in cFos expression profiles in several other regions, including the central amygdala. Finally, chemogenetic stimulation of LH–LHb neurons restored alcohol aversion in Avoiders. Together, these findings implicate a blunted LH–LHb circuit response to alcohol in Avoider rats, which may underlie their reduced sensitivity to alcohol's aversive effects and facilitate post-stress escalation of drinking. We are currently using slice electrophysiology to characterize the responses of LHb and LH-LHb neurons to alcohol in Avoiders, Non-Avoiders, and unstressed Controls.

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S83

A neural circuit pathway for individuality in alcohol preference in Drosophila melanogaster

J.S. Hernandez, N. Le, R. Azanchi, N. Mei, K.R. Kaun

Some people consume alcohol at moderate or even low levels, whereas other people escalate their alcohol consumption until it becomes problematic, contributing to a worldwide biomedical concern over alcohol use and misuse. Very little is understood of the neural substrates underlying individual differences in alcohol preference and seeking, and how escalation arises in some individuals and not others. Investigating the circuits and neural dynamics underlying this individual variation is critical for developing more effective treatments for alcohol use and abuse disorders. We developed an operant paradigm to evaluate the spectrum of behaviors associated with self-administration of a pharmacologically relevant dose of volatilized ethanol in Drosophila. Using genetically encoded calcium sensors, and thermogenetic and optogenetic manipulation of these neurons we discovered high alcohol responsivity is under direct control of a simple two-neuron dopamine-acetylcholine circuit in the Drosophila mushroom body system. Our findings provide a framework to investigate how physiological variability of identified circuits contributes to escalation of alcohol use. Comparing the behavioral and physiological responses of animals that find intoxicating doses of ethanol appetitive or aversive uniquely primes us to examine the mechanisms through which natural and alcohol reward preference manifests in the nervous system.

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Symposium XIX

Translational Studies on the Intersection of Alcohol Use Disorder and Chronic Pain

Chairs: Melanie Schwandt and Vijay Ramchandani

S84

Alcohol as an antecedent for chronic pain: prolongation of hypersensitivity after injury in a mouse model of consumption

Rachel Schorn, Maureen Riedl, Laura S. Stone, Lucy Vulchanova, Anna M. Lee

Chronic pain and alcohol use disorder (AUD) are highly comorbid, with persistent pain common in individuals with AUD, and alcohol used by chronic pain patients for self-medication. Alcohol use increases the likelihood of serious injury and patients with an AUD prior to an injury develop chronic, persistent pain at a higher rate compared with patients without pre-injury AUD. The interactions of chronic pain and voluntary chronic alcohol remain poorly understood, and the effects of chronic alcohol consumption on the transition to persistent pain are largely unexplored at the pre-clinical level. We have developed a model of the transition to persistent pain following voluntary chronic intermittent alcohol (CIA) consumption. Male and female C57BL/6J mice (n=14/group/sex) underwent voluntary CIA consumption in which alcohol-induced hypersensitivity developed after 4-6 weeks of consumption. The degree of alcohol-induced hypersensitivity was not related to the amount of alcohol consumed in either sex. To assess the effect of CIA on injury and pain, we used intraplantar capsaicin and a sciatic nerve crush injury to model short-term and prolonged pain, respectively, after mice had consumed 6-8 weeks of alcohol. In the capsaicin model, water-drinking mice, but not alcohol-drinking mice, recovered from hypersensitivity by 24 hours. In the sciatic nerve crush model, water-consuming mice recovered by 3 weeks post-injury, whereas alcohol-consuming mice showed persistent hypersensitivity, and delayed recovery in mechanical thresholds. Overall, our results suggest that chronic voluntary alcohol consumption facilitates the transition to chronic pain by prolonging hypersensitivity and delaying recovery from injuries.

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S85

Effects of Acute Alcohol Intake on Pain-related Brain Regions and Networks

Jeff Boissoneault, Landrew Sevel, Leah Beissenberger, Aishwarya Belhe, Bethany Stennett-Blackmon

Alcohol has well-documented analgesic effects. In individuals both with and without chronic pain, acute alcohol intake produces significant increases in pain threshold, decreases in pain intensity, and perceived pain relief during laboratory-based quantitative sensory testing. Evidence suggests these effects are dose-dependent, consistent with increased risk for alcohol-related consequences in individuals using alcohol for pain self-management. However, the functional neural mechanisms underlying alcohol analgesia remain poorly understood.
N=97 healthy social drinkers (52.6% women) 21-45 years of age completed two laboratory sessions in which they received placebo or alcohol (.08 g/dL target breath alcohol concentration) in counterbalanced order. ~25 minutes after beverage consumption, they were positioned in a Siemens Prisma 3T MRI. Over each of three task fMRI runs, seven 10s blocks painful heat were applied to the glabrous skin of the foot. Participants rated pain intensity after each stimulus and perceived relief from pain from consuming their beverage after each run. Alcohol-induced change in pain-related functional activation and functional connectivity, including cerebral network topology, was assessed.
Alcohol significant reduced pain-related functional activation of the dorsolateral prefrontal cortex in men, but not women (pFDR=.035). dlPFC connectivity with regions including insula, supramarginal gyrus, and primary motor cortex was also disrupted (pFDR<.024). In addition, alcohol reduced the inter-connectedness of the broader cerebral network (p=.014) and increased the average distance separating network nodes (p=.05) during pain processing. Overall, results provide new evidence that acute alcohol intake significantly perturbs not just localized pain-related functional activation, but also the broad organization of

pain-related cerebral networks.

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S86

Sex differences in chronic alcohol-induced mechanical allodynia: neuroimmune and endocannabinoid system dysregulation in the spinal cord and dorsal root ganglia of dependent mice

Vittoria Borgonetti, Celsey M. St. Onge, Bryan Cruz, Cristina Zalfa, Tali Nadav, Amanda J. Roberts, Tim Ware, Candice Contet, Benjamin F. Cravatt, Michal Bajo, Marisa Roberto

Background: Alcohol use disorder (AUD) is strongly associated with neuropathic pain. Chronic alcohol consumption induces mechanical hypersensitivity, a negative reinforcement mechanism that may facilitate AUD progression. While supraspinal microglia have been extensively studied, their spinal contribution to alcohol-induced pain is less understood. Microgliosis contributes to both alcohol reinforcement and neuropathic pain, and chronic alcohol alters microglial and neuroimmune gene expression. Endocannabinoids (eCBs) modulate mechanical allodynia, but their role in alcohol-related allodynia is unclear. This study investigated mechanical hypersensitivity, spinal microgliosis, neuroimmune mediators, and eCB system alterations in dependent mice, considering sex differences.
Methods: Male and female mice were exposed to the 2BC-CIE paradigm to generate dependent, non-dependent, and naive groups. Mechanical hypersensitivity was measured with Von Frey filaments during withdrawal. Spinal cord and DRG tissues were analyzed for microglial activation, inflammatory markers, and endocannabinoid levels using immunofluorescence and LC-MS/MS. Results: Both male and female Dep mice developed mechanical hypersensitivity during withdrawal, which was reversed by voluntary alcohol consumption; females showed greater improvement. Spinal microglial activation was increased in Dep mice, while Non-Dep microglia showed less reactive states. Particularly, IL-6 expression was elevated in the dorsal horn. Alterations of the eCB system were observed in both DRG and spinal cord and correlated with mechanical hypersensitivity.
Conclusions: Spinal microgliosis and eCB dysregulation contribute to alcohol-induced mechanical hypersensitivity. Modulating neuroimmune pathways may provide a novel, sex-specific strategy to reduce withdrawal-associated pain and relapse risk in AUD.

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S87

Examining the moderating role of intolerance of uncertainty on pain tolerance and craving in patients with chronic pain and alcohol use disorder

Milena Radoman, Emily Heilner, Colleen McGowan, Benazir Neree-Thompson, Elcin Sakmar, Rajita Sinha

Chronic pain (CP) and alcohol use disorder (AUD) frequently co-occur, yet the psychological factors underlying their interaction remain unclear. Intolerance of uncertainty (IU) – a cognitive trait linked to distress in unpredictable situations – may influence pain management and coping behaviors in these populations. This study examined whether IU moderates pain and alcohol craving responses to a pain-related stressor in individuals with CP and AUD. Fifty-five adults aged 18-65 years were enrolled, including individuals with CP only (n=20), AUD only (n=14), CP + AUD (n=8), and healthy controls (n=13). Participants completed a self-report measure of IU and Yale Pain Stress Test (YPST), an adaptation of the Cold Pressor Test, designed to elicit pain-related stress. Behavioral pain tolerance, subjective pain and alcohol craving were assessed across two experimental sessions, one with exposure to an ice-cold water stressor and the second with a warm-water control condition. Exposure to the pain-related stressor significantly reduced behavioral pain tolerance and increased subjective pain across all groups, and also heightened alcohol craving, particularly in individuals with AUD. IU moderated the pain experience during pain-related stress: in the CP + AUD group, higher IU was associated with lower pain tolerance, whereas in the AUD group, higher IU was correlated with greater pain tolerance. IU also moderated craving responses, with higher IU predicting increased craving in individuals with both CP and AUD. These preliminary findings highlight IU as a potential treatment target, suggesting that interventions aimed at improving uncertainty tolerance may enhance pain coping and reduce stress-driven alcohol-seeking behaviors in vulnerable populations.

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POSTERS

P88

Inhibition of cerebrovascular cannabinoid receptor 1 (CB1R) as a potential treatment against alcohol's deleterious effect on fetal cerebral arteries

Shiwani Thapa, Alex Dopico, Anna Bukiya

Alcohol consumption during pregnancy may result in a range of fetal developmental abnormalities termed fetal alcohol spectrum disorders (FASD). FASD remains the leading preventable cause of developmental delays. There is no readily available cure against FASD, though dietary supplementation has been shown to mitigate some consequences of fetal damage by alcohol. The lack of therapeutic breakthroughs largely stems from the complexity of alcohol pharmacodynamics. Neurological delays and psychological deficits have led investigators to concentrate their efforts on identifying functional targets of alcohol actions in the brain while focusing on different neuronal and glial populations. Our laboratory, however, considers fetal cerebral circulation as a critical target of alcohol. In a previous work with baboons, we demonstrated that three episodes of maternal alcohol gavage (rendering 80 mg/dL blood alcohol) during mid-pregnancy downregulated cytoskeletal proteome within fetal cerebral artery, indicating compromised vascularization of the developing brain. Consistently, perinatal fetuses of alcohol-exposed dams exhibited morphometric delay. Both features are characteristic of humans that were exposed to alcohol *in utero*. Here, Doppler evaluation of blood velocity in fetal baboon brain circulation *in utero* showed that alcohol dropped peak systolic velocity by 25%, consistent with alcohol-induced vasodilation. *Ex vivo* alcohol-induced dilation of cerebral arteries from male and female baboon fetuses was blunted by CB1R blocker AM251. Moreover, pilot data indicates that maternal injection with low dose of the CB1R inhibitor rimonabant blunts alcohol effect on blood velocity in fetal cerebral arteries *in vivo*. These results are being validated in larger cohorts and may advance the inhibition of CB1R as a therapeutic strategy against alcohol effect on fetal cerebral artery diameter. Its potential to mitigate proteomic changes and developmental delay is currently being studied.

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P89

Addressing Suicide and Alcohol Use among Alaska Native Young People with Strength-Based Approaches

Stacy Rasmus, Anthony Rodriguez, Elizabeth J. D'Amico, Cyndi Nation, Jim Chaliak

Suicide is the leading cause of death for Alaska Native (AN) young people ages 15 through 24. There is urgent need for culturally appropriate programs, yet only three studies to date have tested suicide prevention interventions among Indigenous people. This presentation details how historical context, including stressors from the legacy of structural racism have increased health disparities among AN young people, and how a community-oriented approach led to an innovative strength-based intervention to address suicide and alcohol misuse among AN young people in Alaska. BeWel (Because We Love You) focuses on providing protective cultural experiences for AN young people to nurture Indigenous identity, building a healthy social network, and increasing intergenerational interconnectedness to reduce risk for suicide and alcohol misuse. Data were collected (n=144, mean age = 18 years, 49% female) across five protective cultural factor (PCF) domains (e.g., connectedness, reasons for life). We compared PCF, alcohol and cannabis use/dependence; anxiety, depression, and health at baseline and 3-month follow-up after BeWeL. Profile 1 (26%) reported relatively low scores across all five PCF domains whereas Profile 2 (74%) reported higher scores. At baseline, Profile 2 was significantly lower than Profile 1 on suicide risk/intention, mental health, alcohol and cannabis use/dependence and reported better general health. At follow-up, Profile 2 was relatively stable; however, Profile 1 improved on all PCF measures and, notably, improved across all substance use and health outcomes. This work provides evidence of the

value and impact culturally adaptive interventions have on reducing risk across a variety of domains.

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P90

Effects of Virtual Culturally Grounded Substance Use Interventions for Urban Native American Emerging Adults: A Randomized Controlled Trial

Elizabeth J. D'Amico, Daniel D. Dickerson, David J. Klein, Anthony Rodriguez, Virginia Arvizu-Sanchez, Kurt Schweigman, Carrie Johnson, Sam Mann, David P. Kennedy, Pierrce Holmes, Alina I. Palimaru, Ryan Brown, Nipher Malika

Although American Indian and Alaska Native (AIAN) people are resilient, they experience numerous health disparities, including high rates of stress, alcohol use and mental health concerns. Urban AIAN emerging adults (age 18-25; N=541) were recruited across the U.S. for a randomized controlled trial from 2020 to 2023. They completed baseline surveys, received either three TACUNA (Traditions and Connections for Urban Native Americans) workshops and a wellness circle, or an opioid education health and wellness workshop, and completed 3-, 6-, and 12-month surveys focused on opioid, alcohol, and cannabis use and consequences; cultural connection, and peer influence. TACUNA utilized motivational interviewing (MI) with a strength based approach focused on connecting with culture (e.g., Native cooking, sage ceremony). TACUNA/Control groups were compared on outcomes using known groups growth mixture models and comparing slope parameters. Compared to control participants, TACUNA participants demonstrated a significantly greater decrease in cannabis use frequency (b= -0.16 vs .09, p<.01), time spent around peers using cannabis (b = -0.10 vs -0.04, p=.03), and anxiety (b = -0.05 vs -0.02, p=.03). Regarding alcohol, TACUNA participants reported a significant decrease in past 90 day alcohol consumption (b= -0.11, p=.01), but control participant drinking remained stable (b= -0.04, p=. 41). Similarly, TACUNA participants reported a significant decrease in largest numbers of drinks in a given day (b= -0.25, p<.01); there was no change in control participant drinking (b = -0.15, p=.09). Findings highlight how an intervention that integrates MI with cultural activities can have protective effects for urban AIAN emerging adults.

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P91

Sex differences in nociceptin and noradrenergic regulation of central amygdala GABAergic transmission in alcohol dependence

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Alcohol Use Disorder (AUD) is a chronic condition characterized by compulsive alcohol-seeking behavior, negative consequences despite use, and a negative emotional state during withdrawal. The central amygdala (CeA) is a key brain hub integrating stress and reward signals. Both pro- and anti-stress neuropeptides, including nociceptin and norepinephrine (NE), dynamically modulate GABAergic transmission in the CeA, impacting relapse and motivational behaviors. Here, we aim to investigate the sex-specific mechanisms underlying the interactions between anti-stress nociceptin and pro-stress norepinephrine on synaptic transmission in the CeA during ethanol dependence and withdrawal in rats. Male and female Sprague-Dawley rats underwent a 4–5 week chronic intermittent ethanol (CIE) vapor paradigm (Dependent, Dep). A subset of these rats underwent withdrawal for 2 weeks of alcohol withdrawal (WD). Control groups were exposed only to air (Naïve). Brain slices were analyzed by whole-cell patch-clamp recordings, evaluating the effects of NE co-applied with nociceptin and vice versa on spontaneous inhibitory postsynaptic currents (sIPSCs) in medial CeA neurons. We found that nociceptin alone consistently reduced sIPSC frequency across sexes and groups. Co-application with NE maintained this inhibition in naïve animals and further decreased sIPSC frequency only in female WD rats. NE alone increased sIPSC frequency only in naïve males and did not affect other groups. However, co-application with nociceptin reduced sIPSC frequency in both sexes under all conditions. These results highlight the complex and sex-dependent interplay between nociceptin and NE in modulating GABAergic transmission in the CeA, highlighting the robust anti-stress role of nociceptin in alcohol dependence and withdrawal.

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P92

Sex hormone regulation of prefrontal cortex parvalbumin interneuron physiology and effects of alcohol

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Sex differences in incidence and pathology of alcohol use disorder are well-documented. Parvalbumin-expressing interneurons (PV-INs) exhibit many sex differences in regulating cognitive and motivated behavior. Our previous studies have identified metabotropic glutamate receptors 1 and 5 as a key molecule mediating sex differences in PV-IN function in binge drinking. PV-INs also express estrogen receptors, which functionally couple with $mGlu_{1/5}$ receptors on the cell membrane. Taken together, we hypothesized that circulating gonadal hormones like estradiol (E2) regulate sex differences in $mGlu_{1/5}$ receptor signaling, and therefore in PV-IN physiology regulating alcohol consumption. We performed *ex vivo* whole-cell electrophysiology in transgenic mice expressing tdTomato in PV-INs, recording from the prelimbic cortex of male and cycling female mice. Estrous stage of female mice was determined by vaginal cytology. In a separate experiment, we optogenetically evoked inhibitory postsynaptic currents (IPSCs) from PV-INs to pyramidal neurons. Brain slices from each mouse were incubated in either standard artificial cerebrospinal fluid (aCSF) or aCSF containing 300nM E2. PV-INs showed greater excitability in E2-incubated female slices. Further, non-estrus female PV-INs had a higher membrane resistance and lower rheobase when incubated in E2, whereas estrus stage females did not exhibit significant differences between incubation conditions. These experiments suggest that E2 modulates the excitability and membrane resistance of PFC PV-INs in an estrous cycle stage-dependent manner. Ongoing experiments aim to assess how E2 alters PV-IN-mediated inhibitory transmission onto pyramidal neurons, repeating experiments in a $mGlu_5$ knockout model, and utilizing pharmacological manipulations to validate the receptor pathways involved in an alcohol model.

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P93

Association of SLC39A8 rs13107325 polymorphism with alcohol consumption

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Genome-wide association studies (GWAS) have identified the SLC39A8 rs13107325 (C>T) variant as a risk locus for alcohol use disorder (AUD). SLC39A8, a highly pleiotropic gene encoding the ZIP8 protein, regulates divalent ion transport, maintains manganese homeostasis, and modulates the NF-κB–mediated pro-inflammatory pathway. The functional consequences of genetic variation in ZIP8 on alcohol behavior remain poorly understood. We retrospectively examined the association between rs13107325 genotype and alcohol-related phenotypes in 660 White/European-ancestry adults who consumed alcohol (CC = 573, CT = 83, TT = 4; 43% female; mean age = 40 ± 14; 26% smokers; mean AUDIT = 15 ± 13). Alcohol consumption was assessed using a 90-day timeline followback, alcohol use problems with the AUDIT, and alcohol sensitivity with the Self-Reported Effects of Alcohol (SRE) scale. General linear models with HC3 robust standard errors were used, including genotype and smoking status as fixed factors, and controlling for age and sex. Compared to CC homozygotes, CT/TT carriers reported significantly lower alcohol consumption (total drinks, drinks per week and drinks per day) and heightened sensitivity to alcohol's effects (SRE total). These effects were only observed among smokers, indicated by significant genotype × smoking status interaction (p's < .05). No group differences were observed on AUDIT. These findings suggest that SLC39A8 variation may contribute to individual differences in alcohol consumption and sensitivity via interactions with smoking. Ongoing work will use a genotype-first, reverse phenotyping approach to better

understand the functional role of ZIP8 in AUD.

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P94

VIP signaling in the prefrontal cortex: an emerging therapeutic target for alcohol use disorder

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Breakthrough treatments are needed to address the public health burden of maladaptive drinking and alcohol use disorder (AUD). Converging evidence implicates prefrontal cortex (PFC) dysfunction in the impaired control and heightened motivation that sustain alcohol use. In the PFC vasoactive intestinal peptide expressing interneurons (VIP-INs) disinhibit pyramidal neurons and shape motivation, processes tightly linked to stress and alcohol, yet the contribution of VIP signaling to alcohol-related behavior is poorly defined. VIP and VIP receptor 1 (VIPR1) are abundantly expressed in the PFC, making the VIP-VIPR1 axis a compelling therapeutic candidate.

Using whole-cell patch clamp in acute prelimbic PFC slices, we find that VIP depolarizes VIP-INs and lowers spike threshold, consistent with increased intrinsic excitability, while exerting minimal effects on pyramidal and SST neurons under the same conditions. This depolarization is VIPR1-dependent: a selective VIPR1 antagonist abolishes the VIP effect. Complementary imaging with the cADDis cAMP biosensor shows that VIP elevates intracellular cAMP in VIP-INs and engages cAMP signaling in pyramidal neurons, indicating pathway activation even where membrane excitability changes are modest.

To establish behavioral relevance, chemogenetic activation of VIP-INs (hM3Dq) increases responding for ethanol in operant self-administration progressive-ratio schedule and reduces social preference, consistent with heightened alcohol-directed motivation. Together, these findings support a model in which VIP→VIPR1 signaling amplifies VIP-IN excitability, enhances cortical disinhibition, and biases behavior toward alcohol seeking.

Ongoing experiments are evaluating the role of VIP in alcohol self-administration using chemogenetics and fiber photometry. This work will evaluate the VIP-VIPR1 pathway as an emerging, druggable target for AUD.

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P95

The cerebellum under stress: Alterations in the cerebellar CRF system following chronic intermittent alcohol exposure

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Alcohol use disorder (AUD) prevalence has risen across the United States following the COVID-19 pandemic. This increase in harmful drinking, particularly among women, is thought to be driven in part by stress-related alcohol use. Corticotropin-releasing factor, or CRF, is a pro-stress neuropeptide that has been implicated in both the physiological response to stress and the development of AUDs. In the central amygdala (CeA), a brain region critical for the negative affect/withdrawal stage of the AUD cycle, CRF1+ neurons exhibit a tonic $GABA_A$ receptor-mediated conductance that is absent in CRF1- neurons. Following chronic alcohol exposure, this tonic inhibition in CRF1+ cells is lost and persists into alcohol withdrawal. Interestingly, cerebellar granule cells (GCs) are densely innervated by CRF-expressing mossy fibers and express CRF1 receptors, yet the impact of chronic alcohol on this system has not been examined. Using electrophysiology, I found that CRF1+ GCs in female mice exposed to chronic intermittent alcohol (CIE) show a significant decrease in spontaneous inhibitory postsynaptic current (sIPSC) frequency, an effect that persists into withdrawal. CRF1- GCs were unaffected. Additionally, RNAscope revealed that Crhr1 and Gabra6 intensity in the cerebellum are significantly increased following CIE. Together, these findings indicate that CIE disrupts CRF/GABA signaling in the cerebellum, paralleling results described in the CeA, and suggest that the cerebellum may therefore contribute to alcohol-dependent behaviors through similar stress and GABA related mechanisms.

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P96

Effects of GLP-1R/GIPR agonism and oxytocin on binge-like alcohol drinking in male and female mice

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Purpose: Increased usage of glucagon-like peptide-1 receptor (GLP-1R) agonists has produced a growing number of reports of reduced alcohol intake in patients, however, the neural mechanism through which these drugs decrease drinking remains unknown. Here we assess the effects of two such drugs on binge-like drinking: semaglutide, a GLP-1R agonist, and tirzepatide, a co-agonist at GLP-1R and glucose-dependent insulinotropic polypeptide receptors (GIPR). Additionally, we investigate the possible contribution of the oxytocin system on this response.

Methods: C57BL/6J mice (n=9-10/sex/dose) underwent drinking-in-the-dark over several weeks to assess effects of multiple doses (0, 0.001, 0.003, 0.009, 0.018, 0.036, 0.072mg/kg) of semaglutide (SEM) and tirzepatide (TZP) on binge-like alcohol consumption. Additional mice received low-dose SEM (0.003mg/kg) with varying doses of oxytocin (0.25, 1, 2.5mg/kg) to assess for synergistic effects of the two drugs.

Results: SEM and TZP decreased alcohol consumption in a dose-dependent manner during both the first and last 2-hr periods of the session ($p < 0.001$). Both drugs exhibit similar potency and efficacy in reducing alcohol intake in both sexes with no sex difference. Low-dose SEM increased the magnitude and duration of oxytocin's effect ($p < 0.05$).

Conclusion: GLP-1R agonists have been reported to decrease alcohol consumption preclinically, however the comparative effects of GIP co-agonism were unknown. We show both semaglutide and tirzepatide significantly reduce binge-like alcohol consumption. Additionally, we show evidence GLP-1R signaling may be acting through the oxytocin system to decrease alcohol drinking; an important step in beginning to elucidate a potential mechanism and pathway through which GLP-1R agonists act to decrease drinking.

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P97

The GLP-1 receptor agonist semaglutide dose-dependently reduces alcohol consumption in Marchigian-Sardinian alcohol-preferring rats

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Glucagon-like peptide-1 (GLP-1) receptor agonists, such as semaglutide, have been shown to reduce alcohol and drug intake and other addiction-like behaviors. However, less is known about the potential role of semaglutide in animal models of high alcohol preference. Here, we investigated the effects of semaglutide on alcohol consumption, anxiety- and stress-related behaviors in the Marchigian Sardinian alcohol-preferring (msP) rats, a well-established model of high alcohol preference. These genetically predisposed animals exhibit excessive voluntary ethanol consumption and pronounced anxious and depressive-like behaviors, providing a valuable translational model for studying alcohol use disorder in vulnerable subpopulations. Adult male and female msPs were given access to 10% ethanol in a two-bottle choice (2BC) paradigm for 1 week to establish baseline drinking. Cohort 1 received 20% ethanol every other day, 2 h/day and was administered semaglutide (0.001, 0.01 and 0.1 mg/kg, s.c.) or vehicle in a counterbalanced Latin square design with 4-day washouts. Cohort 2 underwent a daily 2 h 2BC and received semaglutide (0.01 or 0.1 mg/kg) or vehicle following a between-subjects design. During abstinence, cohort 1 was administered semaglutide (0.1 mg/kg) or vehicle and tested in open field (OF) and acoustic startle, while alcohol-naïve rats (cohort 3) underwent OF, elevated plus maze, and startle. Data from males and females were pooled, as our findings and previous studies have shown no sex differences in semaglutide's effects on reducing binge-like alcohol drinking. Semaglutide reduced alcohol intake in a dose-dependent manner and had anxiolytic-like effects in rats undergoing alcohol withdrawal, while reducing locomotion in alcohol-naïve rats. Future electrophysiological and proteomic studies will identify neural pathways

affected by GLP-1 receptor activation and potential off-target effects.

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P98

Sex-specific modulation of medial prefrontal cortex noradrenergic signaling following voluntary chronic ethanol consumption in mice

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Executive control deficits in individuals with alcohol use disorder (AUD) are linked to dysregulation of the norepinephrine (noradrenaline; NE) stress system. Clinical laboratory trials found that targeting the NE system (e.g. with α1 or β adrenergic receptor antagonists) enhanced drinking outcomes and lowered craving and anxiety in AUD patients. Despite these promising results, the mechanisms by which prefrontal cortex (PFC) circuitry is altered to contribute to cognitive-behavioral outcomes in AUD are not fully understood. We focused on the medial PFC (mPFC) since its prelimbic subregion (PL) promotes drug seeking. First, we examined basal sex differences in the LC→mPFC circuit of C57BL/6J mice using a retrograde fluorescent tracer and found that a greater percentage of LC neurons project to the mPFC in females than males. We then investigated the effects of forced abstinence following two-bottle choice ethanol consumption on NE modulation of mPFC glutamate transmission and adrenergic receptor (AR) gene expression using *ex vivo* electrophysiology and quantitative polymerase chain reaction, respectively. Male mice exhibited reduced NE-evoked glutamate release throughout PL layers 2/3 and 5, alongside increased AR gene expression after 3-5 days of abstinence. Conversely, abstinent females showed enhanced NE-evoked glutamate release specifically in PL layer 5, accompanied by decreased AR mRNA. Current work is using a pharmacological approach to examine which ARs in the PL drive NE-induced glutamate transmission across the sexes. Our findings of sex-specific NE dysfunction can inform comorbid AUD and stress drug discovery.

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P99

BDNF signaling in the central amygdala: Implications for post-traumatic stress and alcohol use disorders

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Post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD) frequently co-occur, while underlying mechanisms of this comorbidity remain unclear. Evidence links brain-derived neurotrophic factor (BDNF) to alcohol dependence severity and relapse, with high BDNF expression in the central amygdala (CeA), a key integrative hub for stress and alcohol dependence. We hypothesized that BDNF dysfunction in the CeA, exacerbated by hyperactive stress signaling, contributes to the pathophysiology of comorbid PTSD/AUD. To test this hypothesis, we implemented a well-established preclinical model in male and female Wistar rats wherein a shock stressor precedes voluntary alcohol consumption and precipitates PTSD-like behavior. We then used a multidisciplinary approach integrating RNA sequencing, qPCR, RNAscope, electrophysiology and pharmacological neuromodulation to assess the role of CeA BDNF in a PTSD/AUD-like phenotype. RNA sequencing revealed significant down-regulation of *Bdnf* in the CeA of alcohol- as well as stress- and alcohol-exposed rats compared to controls. Meanwhile, further quantitative, and spatial analysis with qPCR and RNAscope methods suggested a nuanced, potentially cell-type and sex-specific expression of *Bdnf*. Exogenous application of BDNF on CeA neurons significantly decreased vesicular GABA release during whole-cell patch-clamp recordings of GABAergic miniature inhibitory post-synaptic currents. Pharmacological restoration of BDNF via intra-CeA microinjections prior to alcohol access resulted in reduced alcohol intake. Collectively, these findings suggest that the BDNF system is compromised following stress- and alcohol-exposure, which contributes to the pathophysiology of comorbid PTSD/AUD. Restoration of BDNF-related pathways may represent a promising therapeutic avenue for addressing the intersection of stress and alcohol use.

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P100

Determining sex differences in gene expression patterns following excessive alcohol consumption

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The centrally projecting Edinger-Westphal nucleus (EWcp) is a neuropeptide-rich structure involved in stress and alcohol-related behaviours. Although it plays a critical role in alcohol consumption, the fundamental neurochemical changes induced by alcohol, and whether these differ between sexes, remain poorly understood. This study aimed to determine sex differences in gene expression patterns in the EWcp following binge-like alcohol exposure. Using the 10x Genomics Xenium spatial transcriptomics platform with the base mouse brain panel supplemented with a custom 50 gene panel, we profiled EWcp gene expression in male and female mice compared to alcohol-naïve controls (n=4–7/group). We developed an integrated multi-sample workflow to identify major cell types, perform global and cell type-specific gene expression and pathway analyses, and explore spatial interactions among EWcp populations. Females exhibited basal upregulation of *Vip*, *Crh*, and *Cpne4/6,* compared to males. Alcohol exposure induced transcriptional changes across both sexes, including robust upregulation of *Fos*, consistent with EWcp activation. Notably, *Cpne6* and *Plcxd3* displayed sexually dimorphic regulation, with upregulation in males and downregulation in females. Clustering analyses identified 13 transcriptionally distinct EWcp populations, including peptidergic neurons, microglia, GABAergic and dopaminergic neurons, oligodendrocytes, and several discrete glutamatergic subtypes, within additional basal and sex-specific differences emerged. Future studies will biologically validate these candidate genes to determine their roles in mediating excessive alcohol consumption, providing insight into sex-dependent mechanisms and guiding the development of tailored interventions for alcohol use disorder.

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P101

The role of GluN2A containing NMDA receptors in the central nucleus of the amygdala in the escalation of drinking by alcohol dependent mice

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Ethanol inhibits glutamate activated N-methyl-D-aspartate receptor (NMDAR) currents in areas such as the prefrontal and orbitofrontal cortex and the central nucleus of the amygdala (CeA); an area associated with the negative aspects of alcohol use disorder and withdrawal. NMDARs contain two GluN1 subunits that bind glycine and two GluN2 subunits (A, B, C, D) that bind glutamate with the GluN2A subunit being enriched at glutamatergic synapses. Chronic ethanol exposure up-regulates NMDA receptors and leads to enhanced voluntary consumption of ethanol. The increase in drinking is absent in transgenic mice expressing ethanol-insensitive GluN1 or GluN2A subunits or in mice lacking GluN2A subunits supporting a role of these receptors in alcohol dependence. We hypothesized that GluN2A NMDARs in the CeA are critical for mediating the elevated drinking observed in alcohol dependent mice. To test this hypothesis, mice were infused in the CeA with an Cre-GFP AAV either alone or with a Cre-dependent Cas9-sgRNA-2A AAV to delete GluN2A subunits. In GFP mice, the GluN2A selective antagonist TCN-201 significantly inhibited synaptic NMDA EPSCs but had no effect on those from Cas9-sgRNA-2A mice. NMDA EPSCs in GFP mice were inhibited by acute ethanol and this was reduced in Cas9-sgRNA-2A mice. There was no difference in drinking between air exposed GFP or Cas9-sgRNA-2A mice while chronic exposure to ethanol vapor enhanced drinking in GFP mice. A similar but slightly less robust escalation was observed in Cas9-2A-sgRNA mice suggesting that while CeA GluN2A NMDARs may contribute to enhanced drinking in alcohol dependent mice, this effect likely involves other areas.

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P102

Sodium oxybate attenuates alcohol self-administration in genetically selected alcohol-preferring male and female msP rats

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Earlier studies demonstrated that administration of sodium oxybate (γ-hydroxybutyrate sodium; GHB) attenuates alcohol consumption in rodents and evidence were obtained in male rats only. In the present study, we sought to further investigate the effect of GHB comparing its ability to decrease alcohol drinking in male and female rats. In addition, we plan to study the effect of GHB when alcohol and cocaine are concurrently available.
Male (N = 16) and female (N = 13) genetically selected Marchigian Sardinian alcohol preferring (msP) were trained to self-administer 10% alcohol solution during 30-minute sessions under a fixed-ratio 1 (FR1) schedule of reinforcement. Once stable responding was established, female rats received intragastric (IG) GHB (0, 100, 300, 600 mg/kg), an additional higher dose (750 mg/kg) was given to males. Drug treatment occurred 20 minutes prior to the start of the self-administration session. The experiment was carried out in a within-subject Latin square design. The chronic effect of GHB (0, 300, or 600 mg/kg) on alcohol drinking was also assessed over five consecutive days. This experiment was conducted in a between-subjects crossover design.
Acute administration of GHB significantly reduced alcohol self-administration in both male and female msP rats. At the dose of 600 mg/kg GHB significantly reduced alcohol drinking following both acute and chronic administration. In male alcohol consumption was reduced after administration of 750 mg/kg. To evaluate the therapeutic potential of GHB in polyabuse ongoing studies are investigating its efficacy in rats co-administering alcohol and cocaine.

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P103

Elucidating the role of astrocytic gap junction protein connexin-43 in alcohol drinking

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Connexin 43 (Cx43) is a subunit of gap junction channels and is enriched in astrocytes, where it supports intercellular communication and can be activated by ethanol. In a bulk proteomic screen of parasubthalamic nucleus (PSTN) homogenates, our group identified Cx43 among the most downregulated proteins in alcohol-dependent mice withdrawn from chronic intermittent ethanol exposure with two-bottle choice drinking (CIE-2BC) relative to moderate drinking controls (Air-2BC). Reduced Cx43 levels in CIE-2BC mice were confirmed in an independent cohort by immunoblotting. Prior work shows that ethanol can acutely modulate Cx43-mediated astrocyte signaling, but the functional relevance of CIE-associated Cx43 downregulation remains unclear. We hypothesized that reduced gap junction coupling resulting from decreased Cx43 expression contributes to escalation of alcohol intake. Danegaptide was used as a pharmacological tool to test whether enhancing gap junction function could counteract CIE-associated Cx43 reductions and reduce alcohol drinking. Acute danegaptide administration did not alter intake in CIE-2BC mice but showed a trend toward increasing drinking in Air-2BC mice. Chronic danegaptide treatment did not significantly alter drinking in non-dependent mice, though intake trended higher than vehicle controls. We also evaluated the effects of acute restraint stress in combination with continued chronic danegaptide treatment on ethanol intake. Although restraint did not acutely alter intake, vehicle-treated mice increased consumption on day 2 post-stress, whereas escalation in danegaptide-treated mice was delayed until day 3. Together, these findings suggest that Cx43 is dynamically regulated across dependence and stress states, highlighting astrocytic signaling as a potential interface between alcohol exposure and behavioral state.

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P104

Cocaine and amphetamine regulated transcript II (CART II) signaling decreases ethanol intake in mice

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Alcohol use disorder (AUD) affects millions of people and represents an economic burden to the health system and society. While some FDA-approved medications exist to treat AUD, they are not universally effective across all patients and new therapeutics are needed. Cocaine and amphetamine regulated transcript (CART) produces neuropeptides that have been shown to suppress drug intake and drug seeking behaviors including alcohol. However, the exact role of CART signaling on alcohol intake has been hampered by the lack of a known receptor. We recently identified Lysophosphatidic acid receptor 2 (LPAR2) as the high affinity receptor for CART II in the brain and confirmed in vivo that this receptor mediates CART II anorectic and analgesic effects using validated genetic (LPAR2 knockout mice) and chemical (LPAR2 antagonists) tools. The aim of this study was to investigate the role of CART II-LPAR2 signaling on voluntary ethanol intake by uisng C57BL/6J wild-type (WT) and LPAR2 knockout (KO) mice of both sexes in an intermittent alcohol two-bottle choice (IA2BC) paradigm for several weeks. Control groups receiving sucrose or water in place of ethanol were included in the study. We administered CART II (0.1 μg) via intracerebroventricular injection and observed that CART II suppresses ethanol drinking in wild-type male mice, but not in LPAR2 KO mice. Moreover, LPAR2 KO mice displayed higher baseline ethanol intake and preference. Collectively, these data show a role of CART II-LPAR2 signaling on voluntary ethanol intake opening new venues for novel druggable targets to treat AUD.

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P105

PKCδ neurons in the central amygdala mediate alcohol withdrawal-induced hyperalgesia in female Prkcd-Cre rats

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Chronic pain and alcohol use disorder (AUD) affect millions of individuals worldwide each year. Although alcohol can transiently alleviate pain, its misuse ultimately exacerbates nociceptive hypersensitivity in both humans and animal models as part of the broader alcohol withdrawal syndrome. This bidirectional relationship between pain and alcohol misuse suggests the existence of shared neurobiological mechanisms.
The central amygdala (CeA) plays a pivotal role in multiple stages of AUD, including alcohol abstinence, and in the modulation of pain-related behaviors. Within the CeA, a GABAergic neuronal subpopulation expressing protein kinase C-delta (PKCδ) has been implicated in both alcohol withdrawal in rat models of AUD and in the facilitation of pain-related responses in Prkcd-Cre transgenic mice.
Given the dual involvement of the CeA in AUD and pain, we hypothesized that activation of CeA-PKCδ^{+} neurons constitutes a shared neurobiological substrate underlying both conditions that contributes to alcohol withdrawal-induced hyperalgesia. To test this, we induced alcohol dependence in Prkcd-Cre transgenic female rats using a chronic liquid alcohol diet. During the acute withdrawal phase (24-48 hours post-alcohol cessation), rats exhibited enhanced thermal but not mechanical sensitivity, accompanied by increased PKCδ expression specifically within the CeA. In ongoing experiments, we will employ Cre-dependent inhibitory DREADDs (hM3Di) to dissect the functional contribution of CeA-PKCδ^{+} neurons to alcohol withdrawal–induced thermal hyperalgesia.
These findings identify CeA-PKCδ neurons as key mediators of withdrawal-induced thermal hypersensitivity, revealing a shared neural mechanism between AUD and pain and a potential target for therapeutic intervention.

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P106

Neuroimmune Mechanisms Underlying MDMA-Assisted Therapy in Veterans with Comorbid Posttraumatic Stress Disorder and Alcohol Use Disorder

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The co-occurrence of posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) is highly prevalent in Veterans and contributes to significant declines in health. Current treatment options for comorbid PTSD-AUD remain

limited, with persistent symptomology and high rates of relapse. Both conditions are characterized by aberrant connectivity within cortico-limbic circuits involved in emotion regulation, as well as elevated concentration of metabolites reflecting inflammation in the brain. 3,4-methylenedioxymethamphetamine-assisted therapy (MDMA-AT) is a promising intervention that engages monoaminergic and oxytocinergic systems to enhance emotional processing during therapy. Particularly, MDMA may exert its therapeutic effects by normalizing dysregulated circuits while reducing central and systemic inflammatory signaling. In our open-label pilot study of Veterans with PTSD-AUD (*n=7)*, we conducted functional magnetic resonance imaging (fMRI) and single-voxel magnetic resonance spectroscopy (^{1}HMRS) before and after MDMA-AT to assess changes in resting-state functional connectivity (RSFC) and metabolite concentration. We found a reduction in PTSD severity and alcohol use across participants, as measured by the clinician administered PTSD scale (CAPS) and timeline followback (TLFB) respectively. fMRI analyses revealed reduced RSFC between the amygdala and hippocampus after MDMA-AT, a circuit implicated in threat responses. Complementary MRS data from limbic regions demonstrated a reduction in myo-inositol, an established marker of glial activation. These results suggest that MDMA-AT modulates both functional and chemical indices of neural plasticity and immune activity. Ongoing experiments examine whether MDMA-AT moderate systemic pro-inflammatory signaling from plasma samples. Our findings will highlight the mechanisms engaged by MDMA-AT and support future efforts to identify biomarkers of treatment response.

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P107

Early-life voluntary alcohol consumption impairs cognitive functions in Marchigian Sardinian alcohol-preferring and Wistar rats

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Alcohol use disorder (AUD) is a chronic, relapsing disorder involving compulsive alcohol consumption despite negative consequences. Young adult alcohol exposure is associated with enduring cognitive and affective deficits and increased risk for neurodegeneration. Defining these effects in genetically vulnerable individuals is critical for informing targeted interventions. We used the genetically selected Marchigian Sardinian alcohol preferring (msP) rats, that display excessive alcohol intake, high relapse propensity, and an anxious-depressive-like phenotype. We aimed to compare effects of prolonged alcohol consumption on behavior in msP and non-alcohol preferring Wistar rats. Using the two-bottle choice (2BC) paradigm for five-weeks, where animals had 24 hr access to water and ethanol (20% v/v, or water only; naïve), we then evaluated memory, anxiety, and compulsive-like behaviors; including open field (OF) novel object recognition (NOR) (24hr), Y-maze, light/dark box, and marble burying. MsP rats reliably consumed more ethanol than Wistars, confirming their heightened genetic vulnerability to alcohol. Baseline naïve strain comparison revealed diminished locomotion and increased anxiety phenotype in the msPs, while both strains demonstrated compulsive behavior, and no differences in NOR. Alcohol ameliorated the anxiety phenotype in msPs. Alcohol-exposed rats compared to their naïve strain controls showed decreased locomotion for Wistars and impaired NOR for msPs. Immunostaining in medial prefrontal cortex (mPFC) and hippocampus revealed increased hippocampal microglia and astrocyte density, but not mPFC, of naïve msPs compared to naïve Wistars. Further morphological analyses are underway to identify strain- and alcohol-dependent changes. These results highlight how genetic predisposition and early alcohol exposure may influence neuroinflammation to shape cognitive and emotional outcomes.

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P108

Prenatal Alcohol Exposure Leads to Sleep Disruptions: Implications for Alcohol and Stress

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Sleep is critically important for proper brain development, positive health outcome, and daytime functioning. A growing number of studies suggest that prenatal alcohol exposure alters sleep quality in children. We first examined sleep in children with (PAE) or without (CON) heavy prenatal alcohol exposure using sleep questionnaires, sleep diaries and wearable actigraphy watches for 2 weeks. We found that although sleep duration did not differ between groups, night-to-night variability (sleep time intraindividual variability (IIV)) was greater among children with PAE. Given that sleep quality can impact cognitive and emotional functioning, subjects were also tested on a series of neurobehavioral tasks (NIH Toolbox, BRIEF, CBCL). Path analyses illustrated that sleep quality significantly mediated episodic memory impairments, attention problems, withdrawn/depressed behavior, and increased rule breaking behavior. Significant mediation effects suggest that improving sleep time IIV may influence neurobehavioral functioning in other domains. In addition, using the Oura wearable, our preliminary data indicate that altered sleep architecture persists into adulthood. Thus, prenatal alcohol exposure may lead to long-lasting sleep disruptions. Prenatal alcohol may directly alter brain systems involved in sleep behavior, but there is also a close bidirectional link between sleep and stress, as stress can disrupt sleep and disrupted sleep can worsen stress levels. Thus, there may be links between altered sleep and stress regulation. Moreover, as sleep is a modifiable behavior, interventions targeting sleep problems are critical, as improving sleep quality can consequently ameliorate daytime functioning and health outcomes.

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P109

Shaping Mothers, Shaping Offspring: How Environmental Enrichment Influences Maternal Care under Ethanol Exposure

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The environment plays a decisive role in shaping maternal behavior, with profound consequences for offspring development. Ethanol exposure during the perinatal period is a potent disruptor of maternal care, contributing to fetal alcohol spectrum disorders (FASD). This disruption has been linked to alterations in the oxytocinergic system, a critical regulator of maternal care and social interactions. Here, we investigated whether environmental enrichment (EE) during pregnancy could counteract ethanol-induced impairments in maternal behavior and associated neuroendocrine pathways. Female Swiss mice were housed under standard or enriched conditions and exposed to ethanol from gestational day (GD) 15 to postnatal day (PND) 10. Maternal care was assessed on PND4, followed by analyses of oxytocin (OXT) and estrogen receptor α (ERα) expression in the hypothalamus. Offspring social and aggressive behaviors were later evaluated. Ethanol-exposed dams in standard housing displayed reduced maternal care, whereas EE restored nurturing behaviors. EE also increased hypothalamic OXT expression at PND 11 and PND21 and enhanced ERα expression during late gestation (GD18). Offspring of ethanol-exposed mothers showed social deficits and altered aggression, effects absent when mothers experienced EE during pregnancy. These findings highlight maternal environment as a key determinant of caregiving behavior and offspring outcomes, suggesting that enrichment acts as a protective factor against ethanol-induced disruptions through modulation of oxytocinergic and estrogen receptor signaling.

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P110

Trajectories of interpersonal distress and reciprocal associations with alcohol use in the first year following an alcohol use disorder recovery attempt

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People with alcohol use disorder (AUD) often experience relational conflict, and such interpersonal distress may precipitate behavior change. However, less is known about changes in interpersonal distress after an individual attempts to stop using alcohol, and whether interpersonal distress predicts alcohol use, during the early recovery period (<1 year). The current study characterizes trajectories of experienced interpersonal distress (perceived hostility and rejection) and explores associations between interpersonal distress and recovery outcomes (alcohol problems and percent days abstinent; PDA) among adults reporting a new AUD recovery attempt. Participants (N=501, M_{age}=41.42, 57.50% female) reported general perceived hostility and rejection, alcohol

problems, and PDA at baseline and 1.5-, 3-, 6-, 9-, and 12-months later. Changes in interpersonal distress were characterized with latent curve models, and bivariate latent curve models with structured residuals were used to investigate between- and within-person associations between interpersonal distress and alcohol outcomes over time. Interpersonal distress declined in the first month and remained flat across remaining follow-ups. Those who achieved abstinent remission at 12-month follow-up had a greater reduction in interpersonal distress relative to those who did not. Reductions in interpersonal distress were associated with reductions in alcohol problems and increases in PDA. Greater increases in PDA over time were also associated with accelerated initial declines in perceived hostility that leveled out over time. Early abstinent recovery is marked by reductions in interpersonal distress, and shifts in interpersonal distress appear to move in tandem with changes in alcohol problems and PDA, which may bolster long-term recovery efforts.

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P111

Early Life Stress Increases Activation of Emotion-Associated Regions and Binge-drinking Behavior

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Early life stress (ELS) increases the vulnerability to alcohol use disorder (AUD), yet the basic mechanisms driving this association are unclear. Dysfunction of emotion-associated regions (i.e., insula, basolateral amygdala, hippocampus, and anterior cingulate cortex) influence increased drinking behavior, though ELS effects on this relationship are unknown. We hypothesized ELS-reared mice to have increased activation of emotion-associated regions and binge-drinking behavior. We began by investigating region development using a FosTRAP mouse that allowed for permeant labeling of activated cells during (P10) and after (P21) the limited bedding and nesting (LBN) ELS paradigm. The same animals were exposed to an acute stressor (footshock) at P47, and brains were stained with cFos. To explore the relationship between short and long-term effects of ELS neurocircuitry, LBN-TRAPed cells, acute-stress cells, and coexpression were quantified using whole-brain light sheet microscopy. Following LBN, there was an increase in LBN-TRAPed cells in emotion-associated regions, with decreased anterior cingulate cortex activity following an acute stressor. We next observed the effects of LBN on adulthood binge-drinking. Mice underwent Drinking-in-the-Dark, a binge-like drinking paradigm with an additional week of quinine-adulterated ethanol to measure aversion-resistant drinking. Interestingly, LBN-reared females show increased binge-like consumption even in the presence of an aversive tastant. These results highlight ELS-induced alterations in emotion-associated region development and establish a binge-drinking phenotype in LBN-reared females. Current studies are exploring ELS-induced effects on insular ensemble activity during binge-drinking. Investigation of the neurodevelopmental and behavioral effects of ELS provides insight into novel targets for preventative treatments for AUD.

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P112

Preliminary Evidence that Combination Oral Contraceptive Use in Young Adult Women Is Associated with the Endocrine Stress Response to High-Dose Alcohol

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Introduction: We recently reported that young women's endocrine stress system is less reactive to high-dose alcohol than men's. Since the stress axis is sensitive to gonadal and exogenous steroids, we measured 17-β estradiol (E2) and progesterone (P4) levels in the women prior to ingesting alcohol. This secondary analysis explores whether P4-to-E2 ratios were associated with stress hormone responses.
Methods: 27 women (mean age = 22.1 years) consumed a binge-like dose of alcohol (1.0 ml / kg; 20% alcohol by volume solution). Women were either naturally cycling (NC, N=11), or using combination oral contraceptives (COC, N=7), or long-acting reversible contraceptives (LARCs, N=9). Plasma P4 and E2 concentrations at baseline, and ACTH/cortisol levels over 4h, were measured. After controlling for baseline ACTH/cortisol differences, regression analyses evaluated 1) potential interactions among hormonal contraceptive (HC) groups and P4-to-E2 ratios; and 2) whether those ratios predicted the ACTH/cortisol response to alcohol.
Results: The P4-to-E2 ratio was higher in NC women than women taking HCs ($p=0.034$). Regression results revealed significant interaction effects; P4-to-E2 ratios predicted ACTH ($p=0.009$) and cortisol ($p=0.007$) area-under-curve (AUC) values differently for COC vs. other HC groups. Follow-up regressions demonstrated that among the COC group only, higher P4-to-E2 ratios predicted both higher ACTH AUC values ($p<0.001$) and higher cortisol AUC values ($p=0.031$) with no significant effects for NC and LARC groups.
Conclusions: Although limited by modest sample sizes, these preliminary findings suggest that among women using COCs, the P4-to-E2 ratio is related to the stress hormone response to a binge-like dose of alcohol.

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P113

Reprogramming Microglia to Rescue Negative Affect Due to Binge Ethanol

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Purpose: Negative affect resulting from alcohol misuse contributes to Alcohol Use Disorder (AUD) symptomatology. We recently reported that persistent dysregulation of microglia following binge ethanol promotes long-lasting negative affect. Here, we explore if microglial regeneration can reverse these persistent AUD-related behavioral dysfunction. Further, we aim to determine the underlying mechanisms by which microglial regeneration may improve ethanol-related outcomes.
Methods: C57BL/6J mice were given daily gavages of ethanol (5g/kg, i.g.) or water for 10 consecutive days. Twenty-four hours after the final gavage, mice were subjected to microglia depletion using the colony-stimulating factor receptor 1 antagonist PLX5622 in chow for 3 weeks. Mice were then returned to normal chow for 3 weeks to all for microglial regeneration. Following regeneration, negative affect was characterized using the open field task and fear conditioning with extinction. qRT-PCR was performed for metabolic makers and immunohistochemistry for c-Fos in the infralimbic cortex (IL), a region that promotes fear memory extinction.
Results: Binge ethanol increased novelty induced freezing 8 weeks into withdrawal as well as reduced extinction of conditioned fear memory, which were rescued by microglia regeneration. Ethanol-exposed mice exhibited increased expression of metabolic enzymes which was normalized by regeneration. Ethanol reduced c-Fos in the IL, with improvement by microglia regeneration.
Conclusions: Microglia regeneration improves neuronal dysfunction and reduces negative affect after binge ethanol. Our data suggest this improvement may occur through a metabolic mechanism. Further investigation into the unique metabolic features of regenerative microglia may lead to promising therapeutic targets to improve negative affect related to AUD.

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P114

Developmental characterization of mesoamygdala circuitry and its role in alcohol withdrawal-induced anxiety-like behavior in rats

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Humans with alcohol use disorder often experience negative affect during withdrawal, and anxiety is positively correlated with relapse during abstinence. The neural adaptations that occur during the transition to dependence are not entirely understood, but they may include interactions between mesolimbic reward circuits and brain stress circuits. Previously, we demonstrated alcohol withdrawal-induced activation of ventral tegmental area (VTA) neurons projecting to the central amygdala (CeA), raising the possibility that these cells play a role in the development of withdrawal-associated behavior. Here, we investigated (1) the role of VTA-CeA circuitry in anxiety-like behavior during alcohol withdrawal in adulthood, as well as (2) developmental changes in dopaminergic input into the CeA. Using a dual virus approach to transfect CeA-projecting VTA neurons with excitatory or inhibitory DREADDs, we demonstrate that VTA-CeA circuit activation produces increased anxiety-like behavior in otherwise experimentally naïve adult Wistar rats, and that VTA-CeA circuit inhibition rescues increased anxiety-like behavior during withdrawal from chronic alcohol, indicating a role for VTA-CeA circuitry in increased anxiety-like behavior that

manifests during alcohol withdrawal. Additionally, *in situ* hybridization data in adolescent and adult brains show that expression of CeA *Drd1* increases during development, suggesting that the strength of the VTA-CeA circuit, as well as its influence on anxiety-like behavior, may change developmentally as well. Collectively, the results of these experiments contribute to our understanding regarding the potential role that VTA-CeA circuitry may play in alcohol withdrawal-induced behavior. Ongoing work is focused on detailed circuit characterization throughout development and its impact on anxiety-like behavior.

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P115

Ethanol-induced stress reactivity and the underlying interleukin-1 mechanisms

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Alcohol consumption can be a societal coping mechanism to address stressful situations. Excessive drinking exacerbates the response to stress, which may promote a maladaptive mechanism further increasing alcohol intake to alleviate the heightened stress reactivity. Both alcohol and stress independently activate the neuroimmune system and its master regulator interleukin-1β (IL-1β), suggesting a shared mechanism that may contribute to the stress-induced development of excessive alcohol drinking. IL-1β is a pro-inflammatory cytokine that canonically activates a MyD88-dependent pathway in response to insults (i.e. alcohol and stress). Recently, IL-1β has been found to also activate a neuroprotective PI3K/Akt pathway specifically in neurons. Previous studies have shown that alcohol drinking initiates a switch from the IL-1β-induced neuroprotective pathway towards the pro-inflammatory one, with males more sensitive than females. However, the role of this IL-1β switch at the intersection of alcohol and stress remains unclear. To study this, C57BL/6J mice underwent a chronic intermittent access two-bottle choice alcohol drinking paradigm, paired with an acute restraint stress. We measured anxiety-like behavior using a novelty-suppressed feeding task and found an increase in male alcohol and stress groups. A MyD88 mimetic was used to block the pro-inflammatory IL-1β response, and we observed a reduction in the anxiety-like behavior in the alcohol drinkers. Ongoing studies are investigating possible alcohol-and stress-induced changes in mPFC IL-1R1 receptor expression in neurons, astrocytes, and microglia in a sex-dependent manner. Finally, we are exploring the IL-1R1 receptor regulatory mechanism at mPFC synapses using *ex vivo* electrophysiology in a separate cohort of ethanol-naïve mice.

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P116

Gene expression changes induced by withdrawal in both male and female rat ventral tegmental area: ATAC-seq and RNA-seq analysis

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The ventral tegmental area (VTA) projects to areas of the extended amygdala and is important in the development and maintenance of alcohol use disorders. Alcohol exposure induces neuroadaptive changes in VTA gene expression. We compared differential gene expression in male and female rat VTA during withdrawal to identify common mechanisms of withdrawal-induced changes in VTA physiology. Male and female adult Sprague-Dawley rats were treated with Lieber-DeCarli diet (either 9% v/v alcohol diet or control liquid diet) for 15 days, and two treatment groups were examined: Control diet and 24-hour withdrawal from alcohol diet. ATAC-sequencing (ATAC-seq) or RNA-sequencing (RNA-seq) were performed separately on VTA samples from male and female rats. RNA-seq identified differentially expressed genes (DEGs) in VTA; of 205 genes that were differentially expressed (raw $p < 0.05$) in both male and female VTA, 165 were concordantly regulated: 54 genes downregulated, and 111 genes upregulated. IPA pathway analysis revealed that the downregulated genes were associated with cholesterol/lipid synthesis, whereas upregulated genes were associated with diverse processes. Using ATAC-seq in conjunction with RNA-seq, withdrawal-induced changes in chromatin accessibility were assessed and related to changes in gene expression during withdrawal. Some genes showed high correspondence between ATAC-seq and RNA-seq and between sexes; cholesterol-related genes *Acat2*, *Hmgcr*, and *Idi1* showed relatively high correspondence across groups; other genes showed low correspondence. We conclude that similar DEGs in male and female VTA may point to common neuroadaptive processes that may support the development and maintenance of alcohol use disorder.

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P117

Prelimbic corticotropin-releasing factor: A driving force behind stress-induced alcohol consumption in a mouse model of alcohol use disorder

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Stress is a key risk factor contributing to excessive drinking in individuals with alcohol use disorder. Corticotropin-releasing factor (CRF) is a pro-stress neuropeptide involved in aspects of alcohol and stress responses. Our lab has shown that chronic alcohol and stress activate CRF+ prelimbic (PL) cortex neurons. Here we examined the effects of chronic alcohol and stress on CRF neuron function, how local *Crh* knockdown affects alcohol consumption, and how local inhibition during chronic stress or drinking affects alcohol consumption. All experiments include female and male mice that were exposed to chronic alcohol and stress and endpoints examined changes in physiology or alcohol consumption (2-bottle choice). To accomplish this, we performed whole-cell patch-clamp electrophysiology on CRF+ neurons in the PL of *Crh*-ires-Cre::Ai14 mice, infused *Crh*-Flox mice bilaterally with AAV5-hSyn-eGFP-Cre or AAV8-hSyn-eGFP in the PL, or gave *Crh*-ires-Cre mice bilateral infusions of AAV1-hSyn-DIO-hM4Di or AAV8-hSyn-DIO-mCherry in the PL. Here we show that CRF+ neurons in the PL show significantly increased intrinsic excitability after chronic alcohol and stress exposure. Knockdown of *Crh* in the PL blocks stress-induced escalation of alcohol consumption, and chemogenetic inhibition of PL CRF+ neurons during chronic stress only partially blocks escalated alcohol consumption but preliminary data indicates inhibition during drinking may have a stronger effect. Overall, our data show that chronic alcohol and stress cause hyperexcitability in PL CRF neurons and drives escalated alcohol consumption through a PL CRF-dependent mechanism. Together these data highlight the importance of PL CRF neurons in promoting stress-induced excessive alcohol consumption.

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P118

Reducing effects of the naturally occurring $GABA_B$ receptor agonist, isoliquiritigenin, on alcohol intake and alcohol self-administration in alcohol-preferring rats

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Glycyrrhiza glabra L. (licorice) is a perennial, flowering subshrub in the Fabaceae family. Ethnopharmacological information, as well as several lines of preclinical and clinical evidence, suggest that preparations based on *Glycyrrhiza glabra* exert protective effects against multiple neurological diseases, including drug addiction. The flavonoid, isoliquiritigenin (ISL), is a main constituent of roots of *Glycyrrhiza glabra*. ISL has been reported to behave as a $GABA_B$ receptor agonist and exert multiple pharmacological effects. Given the role of the $GABA_B$ receptor in the neurobiological bases of alcohol use disorder, the present study investigated the effect of ISL on a series of alcohol-related behaviors in female and male Sardinian alcohol-preferring rats. The collected results indicated that: (i) acute treatment with ISL (5-20 mg/kg, i.p.) reduced operant oral alcohol self-administration (under both fixed and progressive ratio schedules of reinforcement) and suppressed cue-induced reinstatement of alcohol seeking; (ii) repeated treatment with ISL (10-40 mg /kg, i.p.) reduced alcohol intake under the limited access, 2-bottle "alcohol *vs* water" choice regimen. ISL effect on alcohol self-administration was (a) partially blocked by pretreatment with the $GABA_B$ receptor antagonist, SCH50911, and (b) potentiated by pretreatment with the positive allosteric modulator of the $GABA_B$ receptor, GS39783. No dose of ISL (20-80 mg/kg, i.p.) altered spontaneous locomotor activity, suggesting the specificity of ISL effect on alcohol-related behaviors. These results closely replicate the well-known suppressing effects of the prototypic $GABA_B$ receptor agonist, baclofen, on alcohol drinking, alcohol self-administration, and reinstatement of alcohol seeking.

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P119

Sex-specific recruitment of Substance P/Neurokinin-1 receptor signaling in central amygdala GABA circuits after chronic alcohol consumption

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Alcohol use disorder (AUD) involves sex-specific remodeling of central amygdala (CeA) circuits, with acute and chronic alcohol exposures producing distinct neuroadaptations in males and females. Accumulating evidence suggests that key stress pathways implicated in AUD pathogenesis are not equally engaged across sexes.

Here, we examined sex-dependent regulation of CeA GABAergic synapses by the Substance P (SP)/neurokinin-1 receptor (NK-1R) system, whose role in AUD has been extensively studied over the last decades. In female alcohol-naïve mice, SP robustly increased CeA GABA transmission, accompanied by stronger NK-1R expression, while the NK-1R antagonist aprepitant decreased it uncovering endogenous SP signaling under basal conditions. In contrast, in naïve males this system is quiescent at baseline but is rapidly recruited by acute *ex vivo* alcohol exposure, enabling both agonist-mediated enhancement and antagonist-induced reduction of GABA transmission.

Chronic alcohol drinking attenuates these baseline sex differences. After alcohol exposure, both sexes exhibit robust SP/NK-1R modulation of CeA GABA transmission; in males, the effect was most pronounced under chronic intermittent (CIE) conditions and was accompanied by increased SP and NK-1R expression. In females, sensitivity to both SP and aprepitant remained high, with no changes in protein expression across continuous or intermittent access.

Our studies identify SP/NK-1R regulation of CeA GABAergic synapses as constitutive in females but alcohol-inducible in males, leading to convergence after exposure, although with stronger CIE-driven recruitment in males, and thus uncover a sex-dependent pathway by which chronic alcohol exposure affects inhibitory tone in the CeA.

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P120

Evaluating drinking behavior and sex-specific adaptations of nucleus accumbens microglia in a fluorescent reporter mouse model of ethanol dependence

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While neuronal adaptations to alcohol exposure have been extensively interrogated, non-neuronal cells, such as microglia, remain relatively understudied. This study utilized male and female fluorescent microglia reporter mice (C57BL/6-Tmem119em2(EGFP)Gfng/J) to evaluate microglial adaptations in the 2-bottle choice (2BC) + chronic intermittent ethanol vapor model of ethanol dependence. Ethanol-treated mice (n=30) exhibited the expected escalation in voluntary drinking (final 2BC bout versus baseline: t_{29}=4.86, p<0.001). Ethanol-naïve control mice (n=30) were subjected to the same procedures, with ethanol omitted. Twenty-four hours after the final vapor exposure, brain tissue was collected or prepared for electrophysiological, transcriptomic, or morphological analyses. Whole-cell patch clamp recordings of Nucleus Accumbens (NAc) microglia in acute brain slices revealed ethanol-induced adaptations. There was an interaction effect of Treatment-by-Sex (p=0.023) on resting membrane potential (Em), driven by a significant effect of Treatment (p=0.011) in females. Voltage clamp experiments indicated a main effect of Sex (p=0.0075), and interaction effects of Voltage Step-by-Sex (p<0.0001) and Voltage Step-by-Sex-by-Treatment (p=0.0163) on current responses to voltage steps. Microglial Em is predominantly regulated by THIK-1, a 2-pore domain potassium channel that also serves as the main contributor to microglial membrane currents overall. Disruption of THIK-1 current is also associated with a variety of activated microglial subtypes. These findings suggest ethanol dependence elicits sex-specific electrophysiological adaptations, potentially disruption of THIK-1, in NAc microglia, and a shift in functional subtype away from homeostasis. Additional insights on sex differences in microglial adaptations and the relationships between electrophysiological properties, morphology, and transcriptional signatures will be provided by immunohistochemical and Tag-sequencing analyses.

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P121

Developmental Alcohol Exposure Decreases Intrinsic Excitability of VGLUT2+ Neurons in the Subiculum of Male Mice

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The subiculum, a key hippocampal output region, is vulnerable to developmental alcohol exposure. The ventral subiculum regulates stress via its connections with the hypothalamus and hypothalamic-pituitary-adrenal axis. The dorsal subiculum (dSub) processes spatial information and contributes to memory consolidation; however, it can also modulate stress through projections to the dorsal septum. Rodent studies have shown that an acute third-trimester equivalent binge-like ethanol exposure increases apoptosis in the dSub, reducing neuronal density into adulthood. This structural damage is linked to impaired spatial working memory. Our work focuses on a subpopulation of pyramidal neurons in the distal dSub that express vesicular glutamate transporter 2 (VGLUT2). These neurons receive input from proximal CA1 hippocampal neurons and project to the granule cell layer of the retrosplenial cortex (gRSC), forming a circuit essential for spatial memory consolidation. VGLUT2+ neurons fire in bursts of 2–4 action potentials when depolarized. We found that, following an 800-pA current injection, ethanol-exposed males showed fewer action potentials per burst (2.33 ± 0.58, n=4) compared to saline-treated males (3.00 ± 0.58; n=14; Two-Way ANOVA: p=0.036). Overall action potential numbers were also reduced in ethanol-exposed males (16.27 ± 5.4, n=4) versus saline (24.8 ± 4.82; n=14; Two-Way ANOVA: p=0.022). We are using optogenetics to further assess VGLUT2+ neuron properties and CA1–dSub–gRSC synaptic transmission. This research aims to further our understanding of how developmental alcohol exposure disrupts subicular function and contributes to FASD-related cognitive impairments and dysregulation of stress reactivity.

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P122

Alcohol withdrawal after chronic intermittent ethanol exposure leads to increased ΔFosB accumulation in the amygdala

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Ethanol is the most abused substance in Brazil and worldwide, associated with numerous health problems, including alcohol use disorders (AUD). AUD are characterized by frequent episodes of compulsion, intoxication, and a negative emotional state during withdrawal. Our study aimed to evaluate and quantify acute and repeated neuronal activation in the amygdala during the ethanol withdrawal period in animals subjected to chronic intermittent ethanol (CIE), using double-labeling immunofluorescence for c-Fos/NeuN and ΔFosB/NeuN. Male C57BL/6 mice were subjected to 6 cycles of 4-day CIE vapor (16h/day) followed by 5-day 2-bottle choice drinking, being allocated into the following groups: CIE vapor exposed (CIE, n=9), control Air exposed (AIR, n=9). Seventy-two hours after the last vapor exposure, the animals were anesthetized and perfused. Next, the brains were collected and stored for subsequent immunofluorescence analysis. CIE animals showed escalation of ethanol consumption across cycles [F(6,96)=10.80; p=0.001]. No significant group differences were found for acute neuronal activation in either the basolateral (BLA) (c-Fos density: F(2,13)=0.8583; p=0.4465) or central amygdala (CeA) (F(2,13)=0.5803; p=0.5736). In contrast, ΔFosB immunoreactivity revealed robust and region-specific effects of CIE. In the basolateral amygdala (BLA), ΔFosB density/mm^2 was significantly higher in CIE mice (β=68.32; p=0.038; F(2,16)=4.356; p=0.03). In the (CeA), ΔFosB accumulation was even more pronounced, with increased ΔFosB density/mm^2 (β=60.47; p=0.0013; F(2,16)=9.576; p=0.0018) and higher $\Delta FosB^+/NeuN^+$ activation percentage (β=8.835; p=0.0046; F(2,16)=7.094; p=0.0062). In conclusion, chronic intermittent ethanol vapor exposure induces persistent neuroplastic adaptations in the amygdala during withdrawal, evidenced by significant ΔFosB accumulation in both the BLA and CeA.

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P123

Change in NAc-mPFC effective connectivity as a predictor of alcohol-induced pain relief

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Perturbations in the nucleus accumbens (NAc)-medial prefrontal cortex (mPFC) connectivity are implicated in alcohol use disorder and the transition from acute to chronic pain, making this circuit of particular interest for gaining mechanistic insights into the self-management of pain using alcohol. The aim of this study was to determine how alcohol-induced change in pain-related NAc-mPFC effective connectivity (EC) relates to pain intensity and perceived pain relief.
97 healthy volunteers aged 21-45 years completed two laboratory sessions where they consumed placebo or active alcohol (0.08 g/dL target breath alcohol concentration). During three task-based fMRI runs, noxious thermal stimuli were delivered to the glabrous skin of the foot using an MR-compatible thermode. Participants rated their pain intensity using an electronic visual analog scale after each stimulus. After each run, participants also rated their perceived pain relief from consuming their beverage. The association of alcohol-induced change in pain-related NAc-mPFC EC with pain intensity and relief was evaluated using generalized psychophysiological interaction (gPPI) analyses.
Decreased pain-related NAc-mPFC EC was a strong predictor of perceived pain relief ($p=0.006;\beta=-0.0006;R2=0.08$), but not intensity ($p=0.54;\beta=0.0003;R2=0.00$) upon alcohol consumption. The association of NAc-mPFC EC with relief was stronger ($p=0.006;\beta=-0.0006;R2=0.08$) than that with the reciprocal mPFC-NAc EC ($p=0.028;\beta=-0.0004;R2=0.05$). Taken together, results indicated that alcohol-induced change in pain-related NAc-mPFC EC is a strong predictor of perceived pain relief, making this circuit a potential therapeutic target for alcohol-related consequences in people with pain.

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P124

The impact of sexual assault on trajectories of sex-related alcohol expectancies

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Introduction: Sexual assault (SA) is a significant public health concern that often involves alcohol. One mechanism of risk for alcohol-involved SA is alcohol expectancies, or beliefs about the effects of alcohol. Sex-related alcohol expectancies (SRAEs) may play a particularly important role. Young adulthood is a period of vulnerability for drinking and SA, and could involve changes in beliefs about alcohol and sex. Yet, no research has investigated whether SRAEs change during this time, and whether SA influences this change.
Methods: Data were collected four times annually, supplemented by assessment "bursts" across 27 weekend days over 9 weekends annually within the 3 interstitial years. Participants reported on alcohol expectancies, drinking, and sexual assault. Four-year trajectories of SRAEs and the impact of SA on these trajectories were examined with latent growth models.
Results: Neither positive nor negative SRAEs changed significantly over the study. SA history (since age 14) did not affect the SRAE trajectories' intercept or slope. Past-year SA assessed annually consistently influenced the intercept of positive and negative SRAEs, but not their slopes. Daily level associations were less consistent.
Discussion: SRAEs are relatively stable throughout young adulthood. However, the level of SRAEs is variable, and may be affected by SA. The timing of SA measurement may play a role: only SA reported concurrent to SRAE assessments were associated with expectancy levels. Expectancy-related interventions may be appropriate for those who have experienced SA, given higher SRAEs within this population. The timeframe of SA measurement should be considered when examining these relationships.

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P125

Sex differences in neural circuits driving binge drinking: A role for the basolateral amygdala

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Binge drinking is the strongest predictor of alcohol use disorder (AUD), yet its neurobiological mechanisms, and potential sex differences in these, remain poorly understood. To address this, we mapped 'activation' of 40 brain regions in male and female alcohol-naïve, alcohol-anticipating and binge drinking mice. Amongst several interesting findings, we identified a sex-specific increase in 'activation' of the basolateral amygdala (BLA) in female binge drinking mice, relative to female naïve ($p=0.003$) and male binge drinking ($p=0.047$) counterparts. Chemogenetic inhibition of the BLA reduced binge drinking in females ($p=0.004$) and trended towards reducing intake in males ($p=0.057$), whilst also reducing natural reward (sucrose) consumption in both sexes (females, $p=0.028$; males, $p=0.005$). We next examined the 'activation' of discrete neurochemical markers (vGlut1, vGlut2, vGAT) and BLA efferent projections to the medial prefrontal cortex, nucleus accumbens core (AcbC) and shell, bed nucleus of the stria terminalis and ventral hippocampus during binge drinking. There were no sex differences in the neurochemical phenotype of 'activated' cells during binge drinking. However, there was preferential 'activation' of the BLA→AcbC projection in female compared to male binge drinking mice ($p=0.003$). Pathway-specific BLA→AcbC inhibition reduced binge drinking in female ($p=0.047$) but not male ($p=0.230$) mice, without altering natural reward intake in either sex (p's>0.05). Collectively, this work highlights the importance of considering sex as a biological variable and adds to the growing literature suggesting distinct neural circuits may drive alcohol-related behaviors between the sexes. The continued investigation of such sex differences may unveil the need for sex-tailored treatments for AUD.

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P126

Withdrawal from chronic ethanol increases interoceptive stress sensitivity in an acid-sensing receptor TDAG8 dependent manner

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Dysregulated interoception associates with alcohol use disorder (AUD). Survival depends on maintaining physiological homeostasis (e.g. neutral pH). Interoceptive (sensing of the body's internal state) threats to homeostasis (e.g. pH imbalance) elicit behavioral, emotional and physiological responses directed toward this goal. Clinical studies use 5-10%CO_2-inhalation (non-hypoxic) as an inducible interoceptive stressor causing acid-base imbalance and panic-relevant fear/anxiety, hyperventilation, hypertension and panic attacks in "CO_2 sensitive" people (e.g those with AUD history). Acutely, ethanol withdrawal increases CO_2-sensitivity, while consumption reduces CO_2-sensitivity. Alcohol is an interoceptive stressor, quickly inducing long-lasting acidosis in plasma/brain that correlates with withdrawal severity. Withdrawal symptoms include these panic-relevant fear/anxiety and physiological effects which contribute relapse risk. Thus, ethanol-evoked acidosis and dysregulated interoception could facilitate a cycle of alcohol use and abuse where drinking occurs to combat negative effects of acidosis during withdrawal. However, the acid-sensing mechanisms driving these effects are unknown. Acid-sensing receptor "T-cell death-associated gene 8" (TDAG8) on blood/brain immune cells regulates CO_2-evoked fear/physiological responses. Here, we developed a novel model to investigate effects of chronic ethanol on CO_2-sensitivity during acute withdrawal. Mice received ethanol for 14d then underwent 5%CO_2-inhalation at 24h withdrawal. In C57BL6/J mice, we found withdrawal from chronic alcohol increased defensive responding to 5%CO_2 and TDAG8 antagonist treatment attenuated this effect. Additionally, TDAG8 knockout mice showed reduced CO_2-evoked hyperventilation. These data suggest ethanol withdrawal increases CO_2-sensitivity in a TDAG8-dependent manner. They point to the translational relevance of this ethanol-CO_2 model to investigate mechanisms underlying AUD interoceptive dysregulation and therapeutic potential of targeting TDAG8.

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P127

Changes in activity across the light-dark cycle during ethanol self-administration, extinction, and ethanol cue-induced reinstatement in male and female rats

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Alcohol use disorder (AUD) patients have a high prevalence of sleep

disturbances and report disrupted sleep as a significant contributor to relapse. To gain more insight into the relationship between alcohol use and disruptions, we designed a study to track activity across the light-dark cycle as a measure of sleep-related endpoints during ethanol self-administration, extinction of self-administration, and ethanol cue-induced reinstatement. Male and female Wistar rats implanted with accelerometer-based telemetry devices were induced to drink ethanol using a sucrose-fade procedure. Ethanol-maintained behavior was extinguished. Alcohol seeking was reinstated by re-exposure to an ethanol-paired cue light. Actigrams (23H) were generated during baseline, acquisition of self-administration, extinction, and reinstatement. Ethanol self-administration increased activity in subjects during the light phase exclusively. In males, the increase was due to decreases in total time inactive and length of longest inactive bout. In females, the increase was due to a decrease in length of longest inactive bout and an increase in latency to the first inactive bout. During extinction, total activity was increased further during the light phase in males; in females, activity normalized in the light phase, but increased in the dark phase that preceded the next operant session. Inactivity parameters during extinction negatively correlated with reinstatement responding. Deleterious changes in activity measures that reflect impairment in sleep-wake cycles were evident in males and females during active ethanol self-administration and extinction of ethanol-seeking behavior. Disruptions in activity measures negatively impacted relapse-like behavior, such that greater disruptions in sleep-related behavior were associated with higher reinstatement rates.

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P128

The effects of acute alcohol consumption on network topographical structure during heat pain processing

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Acute alcohol consumption has profound neurobehavioral effects, including analgesia. This acute alcohol challenge study investigated perturbations in pain-related cerebral network topography using graph theory-based analysis, reflecting global and regional patterns and structures of information processing. Healthy adults (n=97, 51 women, 26.23±4.97 years) completed 2 sessions (acute alcohol [0.08 g/dL target BrAC] or placebo) in counterbalanced order. After dosing, three fMRI runs containing seven blocks of painful heat stimuli applied to the foot were acquired using a Siemens Prisma 3T scanner. Participants reported greater perceived pain relief (0-100 VAS) in the alcohol (38.16 ±21.69) than placebo (15.29±19.25) condition (t=9.57, $p<0.001$). The CONN toolbox was used to assess beverage effects on graph theory metrics for 106 cortical regions of interest. *P*-values were FDR corrected. There was a significant decrease for the interconnectedness between ROIs for the overall network (global efficiency; T_{93}=-2.5, p_{FDR}=0.014) and significant increase in the maximal shortest path length between nodes and the rest of the network (eccentricity; T_{93}=2.33, p_{FDR}=0.02). These changes reflect less efficient information processing and higher resource demands. Additionally, alcohol significantly affected eccentricity, global efficiency, and eigencentrality (connectedness to neighboring nodes that also have high connectedness) for several specific nodes including Heschl's Gyrus, left and right occipital fusiform gyrus, and R cuneus. Taken together, results provide new evidence that alcohol intake produces changes in the overall topography of the cerebral network during pain processing that may at least partially underlie alcohol's analgesic effects.

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P129

Individual differences in stress reactivity and alcohol aversion sensitivity: the role of bed nucleus of the stria terminalis and lateral hypothalamus

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Understanding the neural basis of individual differences in stress coping and subsequent alcohol misuse may inform strategies to treat comorbid stress and alcohol use disorders. In Wistar rats, individual differences in stress coping emerge after exposure to predator odor in a place conditioning paradigm. While some individuals persistently avoid a predator odor-associated context ("Avoiders"), others do not ("Non-Avoiders"), paralleling individual differences in stress reactivity in humans. Importantly, Avoider rats show increased alcohol drinking and prolonged anxiety-like behavior after stress. Here, we tested the hypothesis that Avoider rats also show blunted sensitivity to the aversive effects of alcohol, which may also contribute to their heightened drinking. Using a conditioned taste aversion (CTA) paradigm, we found that Avoiders were indeed less sensitive to alcohol-induced CTA at a dose of 1.5 g/kg. In the brain, we found that an alcohol challenge (1.5 g/kg) suppressed lateral hypothalamic (LH) cFos expression compared to saline in male Avoiders. Additionally, alcohol injection promoted a negative correlation between bed nucleus of the stria terminalis (BNST) and LH cFos expression in Avoiders only. Collectively, these data suggest that promotion of inhibitory neurotransmission in a BNST-to-LH circuit may support a blunted sensitivity to alcohol's aversive properties. We are currently using circuit-based tools to interrogate the role of BNST-LH neurons in avoidance behavior and subsequent alcohol sensitivity and drinking.

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P130

Alcohol-induced conditioned place aversion and cFos expression in the central amygdala-hypothalamic-habenular axis in Avoider and Non-Avoider rats

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Stressful events may increase alcohol misuse in some people, especially in those who respond to stress with avoidance coping. In rats, acute predator odor stress produces persistent avoidance of stress-associated stimuli in a subset of animals termed 'Avoider' rats. Like humans, Avoider rats display escalated alcohol drinking after stress, and prolonged anxiety-related behaviors which may drive drinking via negative reinforcement. In this study, we tested if Avoiders are also less sensitive to alcohol's inherent aversive effect, which may also facilitate heightened drinking. Using a place conditioning paradigm, we found that an alcohol dose of 1.5 g/kg (IP) did not produce place conditioning in Avoider rats but supported conditioned place aversion in Non-Avoiders and unstressed Controls. Using cFos immunohistochemistry, we found that an alcohol challenge (1.5 g/kg) increased cFos expression in the lateral habenula (LHb), an important nucleus for signaling aversive stimuli, in Controls and Non-Avoiders. Interestingly, LHb cFos expression was suppressed by alcohol in Avoider rats. We also quantified cFos expression in two upstream areas that provide dense glutamatergic (lateral hypothalamus, LH) and GABAergic (central amygdala, CeA) inputs to the LHb. While alcohol increased CeA cFos expression across all groups, we found that alcohol suppressed cFos expression in the LH of Avoiders only. We are currently using circuit-based techniques to investigate the role of the LH-to-LHb circuit in avoidance, alcohol aversion sensitivity, and alcohol drinking.

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P131

Central amygdala somatostatin reduces trauma-mediated drinking and modulates GABAergic synapses in a rodent model of post-traumatic stress and alcohol use disorder.

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Central amygdala (CeA) somatostatin (SST) neuropeptide possesses anxiolytic and alcohol-reducing properties, and our hypothesis is that it counteracts overactive stress signaling in post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD). Here, we applied a multifaceted approach to understand SST's role in the expression of PTSD-AUD. Our validated model of PTSD-AUD incorporates a familiar context shock stress paradigm that promotes alcohol drinking for several weeks in rats. This PTSD-AUD model shows persistent increases in neuropathic pain, fear overgeneralization, hyperarousal, and irritability during abstinence from alcohol. The number of cell-specific CeA *Sst*+ transcript levels were decreased and colocalize with the GABA (*Gad2*+) neurons in PTSD-AUD like rats. Similarly, bulk transcript levels for *Sst, Sstr2*, and *Sstr4* were widely impaired in multiple brain sites, including the CeA, of PTSD-AUD rats. In contrast, bulk CeA *Sstr4* transcript levels were increased by AUD alone. Site-specific delivery of CeA SST decreased alcohol drinking but not other measures of PTSD behaviors in PTSD-AUD rats. Electrophysiological data showed that

SST signaling at CeA GABAergic synapses was lost specifically in male PTSD-AUD rats. Collectively, our work provides novel insight into the mechanistic role of SST, distinct sex differences, and SST's therapeutic potential for PTSD-AUD.

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P132

Relationship between patterns of drinking behavior and subjective cognitive decline in midlife and older adults

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Recent epidemiological studies highlight the need to examine drinking patterns as predictors of accelerated cognitive decline in older adults. Subjective cognitive decline (SCD), or self-reported decline in memory and attention without objective evidence of impairment, appears elevated among heavy drinkers. However, few studies have investigated how drinking behaviors (i.e., any vs. binge vs. heavy drinking) relate to SCD in midlife and older adults.

We analyzed responses from adults aged 45 + (n=4465, M_{age}=65.8±11.18, 55.6% women) collected through the Behavioral Risk Factor Surveillance System (BRFSS). A logistic regression examined associations between alcohol use patterns and SCD. The overall model (Block 1) was significant (p=0.006), with any alcohol use showing significantly lower odds (OR=0.76, 95%CI [0.64,0.91], p=0.003) and heavy drinking showing significantly higher odds (OR=1.60, 95%CI [1.06,2.42], p=0.027) of SCD. Interestingly, adding demographic covariates (sex, education, metropolitan status; Block 2; p<.001) removed the protective effect of any drinking (OR=0.86, 95%CI [0.72,1.03], p=0.108). Heavy drinking remained a significant predictor showing 61% greater odds of reporting SCD (OR=1.61, 95%CI [1.06,2.45], p=0.025). Higher education was a strong protective factor (OR=0.65, 95%CI [0.55,0.77], p<0.001). Although both models adequately fit the data (Hosmer–Lemeshow p's>0.05), classification rates remained skewed.

Findings suggest consistent heavy drinking (i.e., weekly) may have a greater influence on perceptions of cognitive decline than other drinking patterns, supporting prior work indicating recent alcohol consumption, rather than lifetime use, may be most detrimental to cognition. Interventions targeting reduced total monthly volume of alcohol consumed may help to mitigate subjective cognitive decline in heavy-drinking older adults.

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P133

Examining PTSD, emotion regulation difficulties, and alcohol use in a community-based sample

Emalee Kerr, Clara Roth, Krstin Naragon-Gainey, Jennifer Read

Prior research has identified difficulties in emotion regulation (DERS) as an important modulating factor in predicting alcohol use among individuals with posttraumatic stress disorder. However, much of the existing research has examined this association in the context of college students, whose patterns of drinking may not generalize to other adult populations. Rates of hazardous drinking and posttraumatic stress symptoms (PTSS) are a relevant in community samples with 25% of adults engaging in problematic drinking and 70% of adults experiencing a traumatic event. In the current study, we sought to expand prior literature by examining the role of emotion regulation in the relationship between PTSS and alcohol use in a community sample. Participants in a mid-sized northeastern city in the U.S. (N=183, Mage=29.9 , 49.5% White) completed a baseline assessment and EMA surveys over 14 days.

Participants reported on PTSS (baseline), DERS (baseline), and drinking outcomes in daily life (drinking urge, alcohol consumption). Findings showed that baseline PTSS (β=2.27, p=.025) positively predicted individual differences in drinking. We also observed a marginally significant interaction between PTSS and DERS scores (β=1.84, p=.068) where the relationship between PTSS and drinking was stronger for those who endorsed greater DERS. This pattern was similar for urge to drink, with significant main effects of PTSS (β=2.04, p=.043), DERS (β=2.12, p=.036), and a significant interaction (β=2.34, p=.020) with a similar pattern. Findings highlight the importance of emotion regulation in treating alcohol use problems in those with a history of trauma and PTSS.

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P134

Longitudinal relations between stress and drinking over a six-year period: Findings from an observational cohort study of high-risk emerging adults

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An extensive literature implicates stress in drinking, but the large majority of studies are cross-sectional, and inconsistent relations have been reported. The relationship may be clarified by longitudinal designs that characterize both stable overall associations and cross-lagged relations that reveal directionality (e.g., does stress at time 1 predict drinking at time 2 or vice versa). We examine this question in a longitudinal observational cohort study of heavy-drinking emerging adults (n=730, 53% female) in 10 waves over a six-year period (age ~21 to ~27) using random intercept cross-lagged panel models (RI-CLPMs). The primary RICLPM suggested a fully constrained model with a statistically significant but small magnitude negative random intercept (-0.12, p = 0.046) but a significant cross-lagged effect of stress on drinking (mean across time = 0.04; range = 0.028 – 0.053, *ps*<.05) i.e., stress predicting increased subsequent drinking over time). Stratification by sex suggested no significant differences, but trichotomizing by coping motives revealed larger relations in the high-coping group. Specifically, the random intercept was substantially larger (-0.3) and the effect sizes of stress forecasting later drinking likewise increased (mean across time = 0.061; range = 0.043 – 0.077, *ps*<.05). These findings reveal divergent patterns of stress in relation to drinking, with inverse relations overall but stress at a given timepoint forecasting subsequent drinking. These findings simply that inconsistent cross-sectional findings may be related to complex divergent longitudinal relations between stress and drinking and are consistent with preclinical findings on neuroadaptive changes in stress biology as drinking progresses.

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P135

Role of the Microtubule Binding Protein, Ninein, in Central Amygdala Modulation of Ethanol Anxiolysis and Consumption

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Rationale: Anxiety disorders increase risk for Alcohol Use Disorder (AUD) and human subjects report that stress and anxiety increase ethanol consumption. The Miles laboratory previously identified the microtubule binding protein Ninein (Nin) as a candidate gene underlying ethanol's acute anxiolytic-like properties in BXD recombinant inbred mice. Here we report that Nin deletion in the central amygdala (CeA) enhances ethanol anxiolysis and decreases ethanol consumption in a sex-specific manner.

Methods: Ninein deletion in CeA was done by stereotactic injections of AAV8-hSyn-GFP (control) or AAV8-hSyn-CRE-GFP (deletion) virus in Ninfl/fl mice. Dependent variables assessed included: ethanol anxiety-like behavior (light-dark box), intermittent access consumption x 5 weeks, sedation (loss-of-righting reflex), quinine and saccharin taste preference and ethanol pharmacokinetics. CeA IPSP activity was measured by voltage clamp analysis in Ninfl/fl mice injected with control (GFP) or Creexpressing viral vectors.

Results: CeA Nin deletion increased acute ethanol anxiolysis (percent time in the light) and reduced ethanol consumption and preference in female but not male mice. Nin deletion did not alter ethanol's sedative hypnotic effects, quinine or saccharin taste preference, or ethanol pharmacokinetics. Preliminary electrophysiology studies on CeA showed Nin deletion alters IPSC duration, suggesting a post-synaptic site of action.

Conclusion: These studies validate Nin as the candidate gene for CeA modulation of acute ethanol anxiolysis and highlight a sex-specific role of Nin in ethanol consumption. Understanding the role of Nin in these behaviors may contribute to future treatment of AUD.

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P136

The effects of sorotonin modulation on acute and chronic alcohol-mediated gabaergic transmission in the central lateral amygdala

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Alcohol is the most widely used addictive substance in the United States, with

approximately 28.8 million individuals meeting criteria for alcohol use disorder (AUD) in the past year. AUD is a chronic, relapsing condition characterized by compulsive alcohol seeking, impaired control over intake, and negative affect during withdrawal. Current treatments remain limited and often ineffective, highlighting the need for new therapeutic strategies.

The central amygdala (CeA), a GABAergic hub within stress and reward circuits, is critically involved in the heightened stress reactivity that drives alcohol use. Serotonergic (5-hydroxytryptamine; 5-HT) projections innervate the CeA, and preclinical and clinical studies indicate that pharmacological manipulation of 5-HT receptors can reduce alcohol drinking. However, the impact of 5-HT signaling on alcohol-mediated GABAergic transmission in the lateral CeA (CeL) remains unclear.

Using electrophysiological, pharmacological, chemogenetic, and RNAscope approaches, we investigated how 5-HT, acute and chronic alcohol exposure, and 5-HT receptor manipulation influence GABAergic signaling in the CeL. We found that alcohol acutely and chronically increases GABA release in the CeL of both naïve and dependent males. In contrast, 5-HT increases GABA release in male naïve as well as female naïve and dependent rats. Targeting 5-HT receptors—via activation of inhibitory subtypes (5-HT1A, 5-HT1B) or antagonism of the excitatory 5-HT2C receptor—blocked alcohol's effects in male naïve and dependent rats.

These findings suggest that serotonergic projections to the CeL contribute to AUD development and reveal sex-specific dynamics in CeL signaling. CeL 5-HT receptors may represent promising targets for AUD treatment

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P137

The impact of intolerance of uncertainty on neural correlates of stress cue reactivity in chronic pain and alcohol use disorder

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Intolerance of uncertainty (IU), a transdiagnostic trait reflecting an individual's tendency to interpret ambiguity as threatening, has been linked to heightened stress responses and problematic alcohol use. However, its role in comorbid chronic pain (CP) and alcohol use disorder (AUD) remains underexplored. We examined whether IU moderated neural responses to stress in 78 adults (CP only: n=23; AUD only: n=19; CP + AUD: n=16; healthy controls/HC: n=20). Participants underwent fMRI scanning while completing a validated cue provocation task involving exposure to standardized stress (S) and neutral (N) cues over six successive runs in a randomized block design. Whole-brain voxel-based 3dLME analysis ($p<.001$, whole-brain cluster correction at $\alpha < .05$) examined condition (N, S) x group (HC, CP, AUD, CP + AUD) x IU interaction, with participant as a random effect and age and sex as covariates. Among individuals with high IU, those with AUD or CP + AUD relative to CP alone showed heightened salience network activation (rostral/dorsal anterior cingulate cortex, anterior insula) during stress versus neutral cues. Additionally, high-IU individuals with CP + AUD compared with AUD alone exhibited increased hypothalamic and decreased ventromedial prefrontal activation in responses to stress versus neutral cues. These preliminary findings indicate that intolerance of uncertainty amplifies stress-related neural dysregulation in individuals with co-occurring CP and AUD, marked by altered salience, hypothalamic, and prefrontal responses. Future work should examine whether reducing intolerance of uncertainty could mitigate stress-related neural responses and improve treatment outcomes in individuals with CP and AUD.

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P138

Adolescent alcohol consumption disrupts prelimbic somatostatin signaling and increases adult female aversion-resistant drinking in mice

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Alcohol exposure disrupts cortical inhibitory somatostatin (SST) neurons. Changes in cortical SST are likely to be involved in the heightened risk of psychiatric disorders seen with chronic alcohol use. Here, we examined SST cell and peptide functioning and related behavioral outcomes after adolescent binge-like drinking. Male and female C57BL/6J and SST-Cre:Ai32 mice consumed alcohol or water in a drinking-in-the-dark (DID) paradigm throughout adolescence (PND 29-54) and were tested for brain SST or behavior changes 30 days after cessation of DID. Generalized linear modeling (GLM) was used to assess sex and alcohol effects while accounting for cohort and litter effects. Prior experiments from our lab found that prelimbic (PL) SST neurons exhibited increased intrinsic excitability after adolescent alcohol consumption. To examine the functional consequences of this PL SST hyperexcitability, we measured the paired pulse ratio (PPR) of SST optogenetic-evoked inhibitory currents onto pyramidal cells, which was reduced after adolescent alcohol consumption (n=10-11, p=0.04). This suggested stronger SST cell-mediated GABAergic outputs to pyramidal cells. We also found that optogenetic-evoked SST peptide release from SST cells was increased in alcohol-exposed mice (n=8-9, p=0.04). We also found that adult females, and not males, exhibited aversion-resistant alcohol consumption after adolescent alcohol exposure (n=9-11, p=0.04), which may be related baseline sex differences in the SST system. We hypothesize that observed behavioral and prefrontal connectivity changes were driven in part via disruption of prelimbic SST signaling. Future work will examine female vulnerability to alcohol and the roles of female-specific variables such as hormonal contraceptives.

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P139

Differential Brain Activation by Voluntary Alcohol Consumption in Male and Female Mice

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Heavy alcohol consumption poses a significant socioeconomic and health burden, yet remains highly prevalent. Clinical studies have demonstrated widespread alterations in brain structure and function following chronic alcohol exposure. In rodent models, ethanol (EtOH) administration induces expression of the immediate early gene c-Fos across multiple brain regions, reflecting enhanced neuronal activity. We hypothesized that short- and long-term EtOH intake differentially affects c-Fos expression in male and female mice. Male and female C57BL/6J and FosTRAP2 mice were given intermittent access to 20% EtOH or water for 24 hours, every other day, over four weeks. During the third session of week one, FosTRAP2 mice received a 4-OHT (tamoxifen) injection to induce ZsGreen expression in c-Fos + cells, enabling within-animal comparison of c-Fos activity after short- and long-access to EtOH. Mice continued intermittent access for three additional weeks and were sacrificed 30 minutes after a final two-hour drinking session. Brains were processed using iDISCO + for clearing and immunolabeling of c-Fos and ZsGreen, followed by light sheet microscopy. Image analysis was performed with ClearMap2, and statistical analysis utilized custom R code. Total whole-brain c-Fos and ZsGreen cell densities were comparable between water and EtOH groups. However, female EtOH drinkers exhibited higher c-Fos + cell density than males. Short-term EtOH exposure led to minimal changes in ZsGreen expression, whereas long-term access produced distinct c-Fos activation patterns across several brain subregions: increased in females and decreased in males. These findings suggest sex-specific network adaptations to voluntary EtOH consumption and highlight potential regions and circuits underlying long-term EtOH intake.

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P140

The combination of the PPARγ agonist pioglitazone and the GLP1R agonist liraglutide act synergistically to attenuate alcohol consumption in genetically selected alcohol preferring rats

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Preclinical evidence shows that activating the GLP-1 receptor with liraglutide reduces alcohol intake and modulates central GABAergic transmission, while activating the PPARγ receptor with pioglitazone decreases alcohol consumption. Since both GLP-1R and PPARγ act as insulin sensitizers, they may share mechanisms linked to glucose regulation. Here, we tested whether combining agents targeting these receptors produces additive effects in reducing alcohol drinking in Marchigian Sardinian alcohol-preferring (msP) rats.

Male (N=18) msP rats, were trained to 10% alcohol operant self-administration. After stable baseline of responding was established, we tested the effect of pioglitazone (0, 10 and 30 mg/kg, os), liraglutide (0, 0.1 and 0.3 mg/kg, sc) and their combination (pioglitazone 10 mg/kg os plus liraglutide 0.1mg/kg, sc).

Subsequently, the effect of chronic administration of the two compounds alone or in combination was evaluated in the two-bottle choice test. Rats were given free choice between water and 10% ethanol for 24 hours a day and drug effect was tested at 2,8 and 24 hours.
Results of the acute treatment show decrease of alcohol consumption when 30 mg/kg of pioglitazone (given o.s.) or 0.1mg/kg of liraglutide (given s.c.) were given. When the two drugs (pioglitazone 10 mg/kg, os; liraglutide 0.1 mg/kg s.c)) were given together the inhibitory of alcohol drinking was significantly more pronounced. In the chronic study coadministration of pioglitazone 10 mg/kg o. s., and liraglutide 0.05 mg/kg s.c, also showed enhanced effect compared to single drug administration.
Our findings show that activation of either PPARγ or GLP-1R reduces alcohol motivation, and their combined activation produces an enhanced effect. Further studies are warranted to clarify underlying mechanisms and potential sex-specific effects.

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P141

The effect of astrocytic Gq-DREADD activation on ethanol consumption and neuroinflammatory changes within the amygdala of female mice

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Ethanol exposure has been shown to alter astrocytic populations and their reactivity within the amygdala, impacting behavioral responses and alcohol consumption. This study investigates the effects of modulating Gq signaling in amygdalar astrocytes in female mice using hM3Dq DREADDs delivered via an adeno-associated viral (AAV) vector system. Female C57BL/6J mice underwent the drinking-in-the-dark (DID) paradigm across multiple cycles. On the final day of the fourth and fifth cycles, clozapine-N-oxide (CNO) or vehicle was administered intraperitoneally 20–40 minutes before ethanol access in a Latin square design. Ethanol intake and blood ethanol concentrations (BECs) were measured. The cohort subsequently underwent additional DID cycles to assess sucrose consumption as a non-alcoholic reward. GFAP-DREADD activation reduced ethanol consumption. In a separate cohort of animals, mice with the GFAP-Gq-DREADD underwent three DID cycles, followed by two intraperitoneal injections of clozapine N-oxide (CNO). Two hours after the final injection, brains were harvested, and amygdala punches were processed for ELISA analysis of proinflammatory cytokines (IL-1β, TNF-α), the anti-inflammatory cytokine IL-10, and brain-derived neurotrophic factor (BDNF), with additional confirmation of DREADD receptor expression. Contrary to our hypothesis, Gq-DREADD activation did not significantly alter cytokine levels in ethanol-exposed mice relative to controls. These findings highlight the role of astrocytic Gq signaling in the amygdala in regulating reward behaviors, but the full mechanism of their action is yet to be determined.

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P142

Insular stress ensembles are directly recruited during ethanol consumption, neurobiologically linking traumatic stress and AUD-related behavior

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The high comorbidity between alcohol use disorder (AUD) and stress disorders underscores the need for targeted therapeutics that address the role stress has on alcohol consumption. While the behavioral link is clear, the neuronal mechanisms driving this relationship are unknown, emphasizing the potential of targeting neuronal ensembles for therapeutic development. To this end, we combined Single Prolonged Stress (SPS), fear conditioning (FC), and varied ethanol exposure times in male and female mice. Behaviorally, SPS disrupted fear discrimination, while ethanol exposure broadly attenuated fear responses. Female mice increased ethanol consumption when access was provided prior to and continuously throughout SPS and FC, contrasting with later exposure. To begin exploring the underlying neurobiological mechanism, we isolated the insular stress ensembles activated during SPS using the genetic knock-in FosTRAP2 mouse model, which created a pharmacologically induced time window to permanently express Cre-recombinase in Fos-activated cells. We then injected a Cre-dependent GCaMP virus and implanted a fiber optic into the insula to 'TRAP' cells during SPS and assess their subsequent activity via fiber photometry. Insular stress ensembles' GCaMP activity increased both at the onset of a struggle bout during restraint stress and at the onset of an ethanol lick during self-administration. This demonstrates that SPS-activated insular cells are directly recruited during subsequent alcohol consumption. This research establishes SPS as a robust translational model and identifies the insular stress ensemble as a critical neurobiological target linking traumatic stress to alcohol-related behavior, paving the way for targeted treatment strategies for stress-induced AUD.

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From Dropout to Retention: Mindfulness-Based Relapse Prevention Shows Promise in Substance Use Treatment in Brazil

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Alcohol use disorder (AUD) is one of the major public health challenges, marked by high rates of relapse and treatment dropout that severely compromise long-term recovery. Emotional dysregulation—characterized by impulsivity, irritability, stress, and anger—has been identified as a key factor associated with these negative outcomes. Previous findings from our group reinforce this evidence, showing that such psychological aspects are strongly linked to both relapse and treatment abandonment. Thus, interventions that strengthen emotional self-regulation may represent promising strategies to enhance treatment efficacy. To address this need, we conducted a randomized clinical trial in two long-term residential therapeutic communities in Brazil. Individuals diagnosed with AUD were randomly assigned to receive either standard treatment (psychoeducation, group therapy, and routine care) or standard treatment plus Mindfulness-Based Relapse Prevention (MBRP). The intervention comprised eight weekly one-hour sessions that included guided meditations, reflective discussions, and experiential practices focused on mindfulness and emotional regulation. Results showed that, compared to the control group, participants in the MBRP group exhibited significantly lower dropout rates ($\chi^2 = 15.0$, $p < 0.001$) and marked reductions in depressive symptoms, impulsivity, stress, and anger expression (wgt% = 72.5, $p < 0.05$). Importantly, anger expression emerged as a key predictor of adherence: MBRP participants reported lower anger levels and greater engagement ($\beta = -0.45$, $p = 0.01$), reflecting longer retention and higher abstinence rates. These findings suggest that mindfulness may modulate the mesocorticolimbic dopaminergic pathway, reducing attentional bias toward alcohol-related cues, facilitating attentional reorientation, and decreasing emotional reactivity. In this context, MBRP stands out as a promising therapeutic adjunct, to be used in parallel with pharmacological interventions, with the goal of enhancing adherence and increasing the likelihood of sustained abstinence.

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Differences in neuronal excitability and response to alcohol in the prelimbic region due to early-life stress

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Both early-life adversity and disruption of monoamine systems are linked to maladaptive aggression and alcohol misuse. The medial prefrontal cortex (mPFC) is responsible for top-down regulation, and ethanol exposure may alter mPFC neuronal excitability, contributing to these maladaptive behavioral phenotypes. Based on prior behavioral findings, we hypothesized that early-life stress (ELS) leads to altered mPFC physiology, producing changes in basal neuronal excitability and response to ethanol, and low-activity monoamine oxidase A (MAOA-L) amplifies these effects. Using ex vivo whole-cell patch-clamp electrophysiology, we recorded Layer V prelimbic mPFC neurons from wildtype (n=10) and genetically-engineered MAOA-L mice (n=14) exposed to ELS (daily maternal separation and a needle poke during postnatal days 3–7) or no stress (NS). During early adulthood, basal excitatory synaptic activity, along with spontaneous and evoked firing were recorded at baseline (6 minutes), followed by ethanol (44 mM) or sham application (15 minutes), and 10-minutes washout. ELS groups exhibited higher membrane resistance and lower resting membrane potential compared with NS during baseline. Ethanol application

increased rheobase (minimum current required to elicit action potential firing) over time in all groups, but only NS mice displayed a significant decrease in input resistance and the number of action potentials in response to ethanol. Genotype effects were not apparent; analysis of spontaneous firing and synaptic activity is ongoing. These findings suggest ELS impacts basal membrane properties and decreases ethanol sensitivity of Layer V prelimbic neurons, indicating early-life neurodevelopmental perturbation leads to long-term physiological alterations that may underlie stress-related alcohol misuse and aggression.

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Table for one: relationships of heavy drinking, loneliness, and stress

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The Behavioral Risk Factor Surveillance System (BRFSS) is the United States' largest nationwide survey of health-related risk behaviors and use of preventative services (CDC, 2025). Recent assessments indicate that although tobacco use has declined in recent years, heavy drinking has increased. This is attributed in part to ongoing stress and loneliness following the COVID-19 pandemic. Despite these trends, research on relationships between heavy drinking, stress, and other health and psychosocial factors remains limited. To address this gap, we obtained permission from the Ohio Department of Health to analyze self-reported 2023 BRFSS data from a sample of 4411 adults (M_{age}= 57.1±17.2, 52% female). Linear regression was run to examine the relationship of heavy drinking and loneliness on stress in the last month with participant age, sex, years of education, income, and chronic pain status as covariates. The overall model was significant (R^2=0.292, p<.001), with older (β=0.018, p<.001), male (β=0.18, p<.001), and higher income (β=0.043, p<.001) participants reporting less stress and participants with chronic pain (β=-0.25, p<.001) and loneliness (β=0.47, p<.001) reporting more stress. No significant effect was found of heavy drinking status (β=-0.040, p=.212) or education (β=-0.0061, p=.715). Post hoc analysis revealed weak but significant correlations between heavy drinking and frequency of loneliness (r=-0.05, p<.001) and chronic pain (r=-0.04, r<.001). Results suggest that adults reporting loneliness and chronic pain may benefit from increased access to strategies for managing stress and drinking behavior. Future studies should explore loneliness and chronic pain as mediators for the relationship of heavy drinking and reported stress.

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Dissecting the functional role of basolateral amygdala CRF neurons in stress and alcohol drinking

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PTSD and AUD often co-occur, posing significant challenges due to limited effective treatments for both conditions. The neuropeptide corticotropin releasing factor (CRF) appears to play an intricate, circuit-dependent role in stress and alcohol-related behaviors. A comprehensive understanding of specific subpopulation of CRF neurons, especially in stress- and alcohol-sensitive brain areas such as the amygdala, is essential for the development of targeted therapies. This study investigated a previously neglected population of CRF-expressing neurons within the basolateral amygdala (BLA). Histological analysis in mice showed that BLA-CRF neurons represent approximately 3% of the total neuronal population and display unique characteristics, such as increased excitability and heightened firing rates. Projections from the insular cortex (IC), associated with interoception, functionally connect to BLA-CRF neurons. Initially, these IC inputs exhibited low efficacy on CRF neurons; however, they were significantly augmented in mice subjected to repeated social defeat stress (SDS). Next, to determine the functional roles of BLA-CRF neurons in alcohol consumption, we manipulated BLA-CRF neuronal activity during a homecage alcohol drinking paradigm. While activation these neurons did not alter alcohol intake in either control or SDS mice, inhibition successfully prevented the stress-induced escalation of alcohol intake in SDS mice, not in controls. Collectively, the findings indicate that repeated stress experiences augment BLA-CRF neuronal activity through IC-BLA projections. This augmented functional connectivity promotes the stress-induced increase in alcohol consumption. These results offer mechanistic insights into a top-down controlled, neuropeptide-expressing neuronal population in the amygdala, providing a promising target for therapeutic interventions in co-morbid PTSD and AUD.

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External Globus Pallidus Arkypallidal Circuit Dynamics Gate Risk-Taking Behavior

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Npas1+ arkypallidal neurons are a distinct subtype of neurons located in the external globus pallidus (GPe), a key component of the basal ganglia. These neurons, characterized by their expression of the transcription factor NPAS1, play a significant role in modulating inhibitory motor sequences and behavioral control. Npas1+ neurons are known to suppress locomotion, contrasting with parvalbumin-expressing neurons in the GPe, which promote movement. This suppression is crucial for action inhibition and is thought to provide a "cancelling signal" that can abort upcoming or ongoing actions, thereby regulating motor output and maintaining behavioral control. In this study, we investigated the involvement of Npas1+ neurons in risky behaviors and examined whether their activity is altered by alcohol consumption. To this end, we expressed the calcium indicator GCaMP8F exclusively in Npas1+ GPe neurons and recorded their calcium activity both locally in the GPe and in the dorsal striatum (DS), where their terminal fields are located. Using in-vivo fiber photometry combined with behavioral video tracking, we assessed risk-related behaviors in animals using the elevated plus maze and elevated zero maze. Using pose estimation to home in on specific behavioral sequences, we found that Npas1+ neuron activity predicts and scales with risk assessment behavior. Furthermore, chemogenetically activating or inhibiting Npas1+ neurons bidirectionally altered risk-associated behavioral sequences. These preliminary findings suggest that Npas1+ arkypallidal neurons encode the magnitude of environmental risk and modulate risky behaviors, which are known to be disrupted by alcohol exposure. Collectively, this work identifies a novel subclass of neurons that encode risk taking strategies and are implicated in the development of alcohol use disorder. Understanding the distinct roles of Npas1+ neurons in action inhibition provides valuable insights into their involvement in motor control and behavioral regulation in the context of alcohol use disorder. This research underscores the importance of these neurons in both normal and pathological states.

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