BBC Publications

BBC 2011

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Zorrilla EP, Heilig M, de Wit H and Shaham Y (2013) **Behavioral, biological, and chemical perspectives on targeting CRF1 receptor antagonists to treat alcoholism.** *Drug and Alcohol Dependence* 128, 175-86. PMC3596012

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BBC 2015

Grandy DK, Miller GM and Li JX (2016) **"TAARgeting addiction"– The Alamo bears witness to another revolution.** *Drug and Alcohol Dependence*. 159, 9-16. PMC4724540

BBC 2016

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Acknowledgements

Sponsors

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Nora Charles
Gregory Collins
Rajeev Desai
Lindsey Galbo-Thomma
Sally Huskinson
Brian Kangas
Thomas Keck
David Maguire
Jacques Nguyen
Alexa-Rae Wheeler

Presentation Judges

Kelly Berg
Carlos Bolaños Guzmán
Nora Charles
Greg Collins
Rajeev Desai
Andrew Eagle
William Fantegrossi
Carrie Ferrario
Michael Gatch
Katherine Goldey
Takato Hiranita
Sally Huskinson
Brian Kangas
Thomas Keck
Mei-Chuan Ko
Jun-Xu Li
Travis Moschak
Kevin Murnane
Alan Myers
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Steven Nieto
Linda Perrotti
Ritu Shetty
Justin Strickland
Zijun Wang
Hideaki Yano

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Julia R Taylor

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Lee Gilman
KC Leong
Justin C Strickland

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Cassandra D Gipson-Reichardt
Sally L Huskinson
Brian D Kangas
David N Kearns
Vanessa Minervini
Jacques D Nguyen

Maharaj Ticku Memorial Travel Fellowship for New Investigators

2012 – Jun-Xu Li
2013 – Kevin B Freeman
2014 – Christopher W Cunningham
2015 – Brian D Kangas
2016 – Clinton E Canal
2017 – Thomas M Keck
2018 – Comfort A Boateng
2019 – Stephen J Kohut
2020 – Lee Gilman
2022 – Corinde E Weirs
2023 – Justin C Strickland
2024 – Zijun Wang
2025 – Jacques D Nguyen

Abby Loudermilk Travel Award

Abby Adair Loudermilk (1979-2018), lawyer, writer, and community volunteer, obtained her law degree at St. Mary's University and had her own private practice. She was known for her sharp wit, boisterous laugh, and her kind, compassionate spirit. Had her life not been cut short by addiction, Abby would still be supporting people today in ways big and small. The Abby Loudermilk Travel Award, established by her lifelong friends in memory of Abby's generous spirit, supports attendance of a graduate student and a postdoctoral fellow that self-identify as women, and who are researching substance use disorders using female subjects, at the annual meeting of Behavior, Biology, and Chemistry: Translational Research in Substance Use Disorders.

Predoctoral	Postdoctoral
2022 – Kimberly M Holter	2022 – Renata Christina Nunes Marchette
2023 – Gwendolyn Burgess	
2024 – Cristina Rivera Quiles	2024 – Laia Castell Almuni
2025 – Alexa-Rae Wheeler	

Travel Awardees

Abdul Rahman Abbas
Valeria Acosta
Tiffany Aguirre
Mariam AlAdsani
Saghir Ali
Manuel Alvarez
Nina Beltran
Brissa Black
Abigail Bowring
Taylor Bratkovich
Aditi Buch
Astrid Cardona-Acosta
Teresa Cho
Leonardo Clark
Tracie Crenshaw
Anthony Cuozzo
Parth Dangore
Isabella Davis
William Doyle
Soren Emerson
Jade Escarsega
Troy Fort
Kofi Frimpong-Manson
Isabel Gallinger
Adrianne Garrett
Abhishek Gour
Stephanie Hockett
Payton Kahanek
Simranjeet Kaur
Nishtha Khanna
Lida Khodavirdilou
Nana Kofi Kusi-Boadum
Michael Leonard
Melissa Lewis
Mengchu Li
Dar-Yin Li
Dylan Lifshitz
Annie Lin
Ravleen Liu
Hayley Manke
Harlie McKelvey
Kathleen McNealy
Noëlle Meisser
Devin Morrisson
Gabriela Naime
Lewis Nunez Severino
Henry Oo
Bethany Pierce
Zachary Pierce-Messick
Tristan Polton
Austin Pothikamjorn
Justin Pressley
Joshua Prete
Angelica Romero
Raina Runk
Mahfuz Sakib
Lauren Scrimshaw
Taylor Simmons
Marina Smoak
Leslie Sullivan
Davis Van Dyk
Adriana Vasquez
Allison Volf
Brandon Wallroff
Alexa-Rae Wheeler
Shuwen Yue

Program Overview

FRIDAY 21 MARCH 2025

3:00 PM – 6:00 PM	Registration – Embassy Landmark, Bluebonnet Foyer	
4:00 PM – 6:00 PM	Pathways to Careers in Science Workshop – Embassy Landmark, Bluebonnet AB	
6:00 PM – 8:00 PM	BBC Opening Reception and Networking – Embassy Landmark, Bluebonnet Foyer	

SATURDAY 22 MARCH 2025

8:00 AM – 8:05 AM	Welcome and Opening Remarks	
8:05 AM – 10:05 AM	Plenary Symposium: ***PK Approaches to Treating Substance Use Disorders*** **Sandra Comer** | Columbia University *Vaccines for the treatment of opioid use disorder: Preliminary clinical data* **Kim Janda** | Scripps Research Institute *A pharmacokinetic strategy to combat the ultra-potent opioids* **Chang-Guo Zhan** | University of Kentucky *Development of efficient enzyme therapies for cocaine use disorders* **Xinhua Li** | Clear Scientific *A broad-spectrum therapeutic for acute opioid and stimulant intoxication*	Chair: Gregory Collins
10:05 AM – 11:35 AM	Poster Session I and Refreshments	
11:35 AM – 12:50 PM	Lunch	
12:50 PM – 2:20 PM	Open Oral Communications I	Chairs: Lindsey Galbo-Thomma and Brian Kangas
2:20 PM – 3:50 PM	Poster Session II and Refreshments	
3:50 PM – 5:20 PM	Open Oral Communications II	Chairs: Alexa-Rae Wheeler and Carlos Bolaños Guzmán
5:20 PM – 5:30 PM	Refreshment Break	
5:30 PM – 6:30 PM	Special Lecture **Kerry Ressler** | McLean Hospital – Harvard Medical School *The intersection of trauma, PTSD, and addiction*	Chair: Rajeev Desai
6:30 PM – 7:30 PM	Cocktail Hour and Poster Viewing	
7:30 PM – 9:30 PM	Dinner and Science Trivia	

SUNDAY 23 MARCH 2025

8:15 AM	Travel Awardee Group Photo	
8:30 AM – 10:00 AM	Open Oral Communications III	Chairs: Jacques Nguyen and Sally Huskinson
10:00 AM – 10:10 AM	Refreshment Break	
10:10 AM – 11:40 AM	Open Oral Communications IV	Chairs: Thomas Keck and Nora Charles
11:40 AM – 11:50 AM	Refreshment Break	
11:50 AM – 12:50 AM	Special Lecture **Jane Aldrich** | University of Florida *Optimizing macrocyclic peptides as potential treatments for substance abuse*	Chair: David Maguire
12:50 AM – 1:05 PM	Travel and Presentation Awards	
1:05 PM	Adjournment	

Maharaj Ticku Memorial Travel Fellowship for New Investigators Awardee Abby Loudermilk Travel Awardee BBC Travel Awardee

Program Details

Friday 21 March 2025

Registration	3:00 PM – 6:00 PM	*Bluebonnet Foyer*
Pathways to Careers in Science Workshop	4:00 PM – 6:00 PM	*Bluebonnet AB*
Opening Reception	6:00 PM – 8:00 PM	*Bluebonnet Foyer*

Saturday 22 March 2025

Complimentary Breakfast	7:30 AM	*Breakfast Café*
Welcome and Opening Remarks	8:00 AM – 8:05 AM	*Bluebonnet AB*
Plenary Symposium	8:05 AM – 10:05 AM	*Bluebonnet AB*

PK Approaches to Treating Substance Use Disorders
(Chair: Gregory Collins)

8:05 AM – 8:35 AM **Sandra Comer** | Columbia University
Vaccines for the treatment of opioid use disorder: Preliminary clinical data

8:35 AM – 9:05 AM **Kim Janda** | Scripps Research Institute
A pharmacokinetic strategy to combat the ultra-potent opioids

9:05 AM – 9:35 AM **Chang-Guo Zhan** | University of Kentucky
Development of efficient enzyme therapies for cocaine use disorders

9:35 AM – 10:05 AM **Xinhua Li** | Clear Scientific
A broad-spectrum therapeutic for acute opioid and stimulant intoxication

Poster Session I and Refreshments (odd posters judged)	10:05 AM – 11:35 AM	*Bluebonnet C/Lantana*
Lunch	11:35 AM – 12:50 PM	*Bluebonnet AB*
Oral Communications I	12:50 PM – 2:20 PM	*Bluebonnet AB*

(Chairs: Lindsey Galbo-Thomma and Brian Kangas)

12:50 PM – 1:05 PM **Troy Fort** | Kansas State University
The effect of methamphetamine self-administration and URB597 treatment on cannabinoid receptor expression and anandamide concentrations

1:05 PM – 1:20 PM **Soren Emerson** | Vanderbilt University
Histone acetyltransferase KAT2A is a critical mediator of drug-associated learning and transcription in the nucleus accumbens

1:20 PM – 1:35 PM **Bo Wood** | LSU Health Sciences Center Shreveport
Sex-Dependent Effects of 2,5-Methoxy-4-Iodoamphetamine (DOI) on Methamphetamine Self-Administration: Mechanistic Insights from Antagonism and PET Imaging Studies

1:35 PM – 1:50 PM **Adriana Vasquez** | University of Texas at Austin
Effects of oral hormonal contraceptives on amphetamine-seeking behavior

1:50 PM – 2:05 PM **Kathleen McNealy** | University of Nebraska – Lincoln
Impacts of contraceptive hormone ethinyl estradiol on the primary reinforcing and reinforcer-enhancement effects of nicotine

2:05 PM – 2:20 PM **Nana Kofi Kusi-Boadum** | University of North Texas Health Science Center
AT-1001, a potential therapeutic agent for smoking cessation

Maharaj Ticku Memorial Travel Fellowship for New Investigators Awardee | Abby Loudermilk Travel Awardee | BBC Travel Awardee

Poster Session II and Refreshments (even posters judged) 2:20 PM – 3:50 PM *Bluebonnet C/Lantana*

Oral Communications II 3:50 PM – 5:20 PM *Bluebonnet AB*

(Chairs: Alexa-Rae Wheeler and Carlos Bolaños Guzmán)

3:50 PM – 4:05 PM **Brissa Black** | McLean Hospital – Harvard Medical School
Effects of Chronic Fentanyl Exposure in Squirrel Monkeys

4:05 PM – 4:20 PM **Alexa-Rae Wheeler** | University of Texas at Austin
Relationships between fentanyl self-administration and risk-taking behavior in rats

4:20 PM – 4:35 PM **Brandon Wallroff** | University of Nebraska Omaha
Sex differences in the effects of serotonin-2A activation on fentanyl demand in Sprague-Dawley rats

4:35 PM – 4:50 PM **Harlie McKelvey** | Wake Forest University School of Medicine
Characterizing Sleep Disruptions Associated with Morphine-Dependence and Spontaneous Withdrawal in Rats

4:50 PM – 5:05 PM **Mengchu Li** | University of Michigan
An orally available negative allosteric modulator of mu-opioid receptor precipitated minimum withdrawal symptoms and reversed fentanyl's effects in drug discrimination

5:05 PM – 5:20 PM **Jacques Nguyen** | Baylor University
Investigating Opioid and Nicotine Effects on Perineuronal Net Structures in Wistar Rats

Refreshment Break 5:20 PM – 5:30 PM

Special Lecture 5:30 PM – 6:30 PM *Bluebonnet AB*

Kerry Ressler | McLean Hospital – Harvard Medical School
The intersection of trauma, PTSD, and addiction
(Chair: Rajeev Desai)

Cocktail Hour and Poster Viewing 6:30 PM – 7:30 PM *Bluebonnet C/Lantana*

Dinner 7:30 PM – 9:30 PM *Bluebonnet AB*

Science Trivia *Bluebonnet AB*

Sponsored by CPDD - Join us for an hour of fun, science, trivia, and prizes!

Maharaj Ticku Memorial Travel Fellowship for New Investigators Awardee | Abby Loudermilk Travel Awardee | BBC Travel Awardee

Sunday 23 March 2025

Complimentary Breakfast — 7:30 AM — *Breakfast Café*

Travel Awardee Group Photo — 8:15 AM — *Hotel Lobby*

Oral Communications III — 8:30 AM – 10:00 AM — *Bluebonnet AB*

(Chairs: Jacques Nguyen and Sally Huskinson)

8:30 AM – 8:45 AM — **Siddappa Byrareddy** | University of Nebraska Medical Center
Substance use and SIV infection in macaques ameliorate a cerebrospinal fluid single-cell transcriptomic profile associated with neurocognitive impairment

8:45 AM – 9:00 AM — **Isabel Gallinger** | Wake Forest University School of Medicine
Diurnal variation in striatal acetylcholine release and Pavlovian behavior

9:00 AM – 9:15 AM — **Simranjeet Kaur** | Texas Tech University Health Sciences Center
Chronic exposure to arsenobetaine in mice is associated with cognitive impairments and changes in brain gene expression

9:15 AM – 9:30 AM — **Lauren Scrimshaw** | Kent State University
Investigating how chronic stress exposure in rats sex-specifically affects willingness to work for sweet + salty reinforcers and overall home cage salt consumption

9:30 AM – 9:45 AM — **Shuwen Yue** | University of Kansas
Insulin-like growth factor 1 and its receptor in prefrontal cortex regulates heroin addiction-induced behavioral and synaptic plasticity

9:45 AM – 10:00 AM — **Michael Leonard** | Vanderbilt University
The effects of cocaine delivery rate on drug-conditioned behavior and neural dynamics in the nucleus accumbens

Refreshment Break — 10:00 AM – 10:10 AM

Oral Communications IV — 10:10 AM – 11:40 AM — *Bluebonnet AB*

(Chairs: Thomas Keck and Nora Charles)

10:10 AM – 10:25 AM — **Justin Pressley** | University of Arkansas for Medical Sciences
In vivo and in vitro drug-drug interactions between synthetic cannabinoid receptor agonists and psychiatric drugs

10:25 AM – 10:40 AM — **Abigail Bowring** | Texas A&M College of Medicine
Prenatal alcohol and cannabinoid exposures impose distinct, sex-specific epigenetic signatures of alcohol-seeking behaviors in adult mice

10:40 AM – 10:55 AM — **Joshua Prete** | Wake Forest University School of Medicine
Cognitive effects of chronic ethanol drinking in male and female monkeys

10:55 AM – 11:10 AM — **Marion Friske** | University of Texas at Austin
Molecular mechanisms underlying TLR7-induced increases in voluntary alcohol consumption in C57BL/6J mice

11:10 AM – 11:25 AM — **Zachary Pierce-Messick** | Johns Hopkins University School of Medicine
Engagement in non-drug activities is inversely related with alcohol demand

11:25 AM – 11:40 PM — **Hideaki Yano** | Northeastern University
Highly efficacious synthetic cannabinoid receptor agonists containing l-tert-leucinate and an antidote approach against them

Maharaj Ticku Memorial Travel Fellowship for New Investigators Awardee | Abby Loudermilk Travel Awardee | BBC Travel Awardee

Refreshment Break	11:40 AM – 11:50 AM	
Special Lecture	11:50 AM – 12:50 PM	*Bluebonnet AB*

Jane Aldrich | University of Florida

Optimizing macrocyclic peptides as potential treatments for substance abuse

(Chair: David Maguire)

Travel and Presentation Awards	12:50 PM – 1:05 PM	*Bluebonnet AB*
Adjournment	1:05 PM	

See you at BBC 2026!

Menu Overview

Complimentary breakfast served by the Embassy Suites weekdays 6:30 – 9:30 AM and weekends 7:30 – 10:30 AM.

Friday Dinner Reception – **Taste of Mexico Buffet**

Mexican Spring Mix Salad

Beef Fajitas with Grilled Peppers and Onions

Pollo Asado – Grilled Chicken

Cilantro Lime Rice, Charro Beans

Dulce de Leche Cheesecake

Saturday Lunch – **Southern Flavors Buffet**

Farmer's House Salad

Smoked Beef Brisket

Marinated Barbecue Chicken

Garlic Mashed Potatoes, Southern Style Green Beans

Bourbon Street Pecan Pie

Saturday Dinner – **Italian Reception***

Crispy Romaine Caesar Salad

Breaded Chicken Topped with Tomato Basil Sauce and Mozzarella

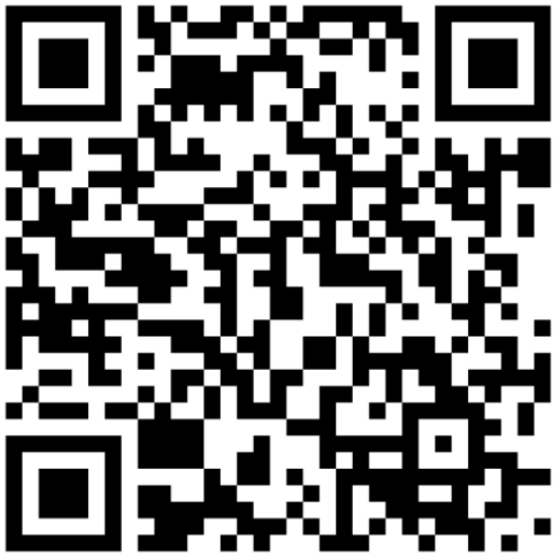
Garlic & Herb Linguini, Grilled Asparagus

Tiramisu Bistro Cake

Layered Lemon Bistro Cake

For those with dietary restrictions, please utilize the colored table tent provided

SCAN



To view the whole program

Oral Communications

Oral Communication 1-1

The effect of methamphetamine self-administration and URB597 treatment on cannabinoid receptor expression and anandamide concentrations

Fort, Troy D.[1]; Azuma, Miki C.[1]; Rigler, Jocelyn H.[1]; Ayers, William[1]; Cain, Mary E.[1]

[1]Department of Psychological Science, Kansas State University, Manhattan, KS, USA

Overdose deaths due to methamphetamine (meth) have risen significantly in the last decade. One system of therapeutic interest for reducing relapse is the endocannabinoid (eCB) system, specifically anandamide (AEA). Inhibiting the metabolizing enzyme of AEA, fatty-acid amide hydrolase (FAAH), using URB597 has shown efficacy in attenuating cue-induced relapse for cocaine and nicotine. We evaluated whether the efficacy of URB597 extends to cue-induced meth relapse and what effect meth abstinence and URB597 treatment has on eCB and glutamate receptor expression. 48 male Sprague-Dawley rats self-administered either meth (0.1 mg/kg/infusion) or saline for 6 hours per day for 12 sessions. Following the self-administration period, rats entered a forced abstinence period where they were not exposed to meth or meth-related cues. Rats were given daily injections of either URB597 (0.3 mg/kg or 1.0 mg/kg; ip) or vehicle during the abstinence period. Cue-seeking was tested on Withdrawal Days (WD) 2 and 28. Following the cue-seeking test, brains were prepared to measure receptor expression and AEA concentrations via western blot and ELISA, respectively. URB597 was ineffective in attenuating cue-induced craving at either WD2 or WD28. Meth abstinence significantly decreased cannabinoid receptor-1 (CB1) expression in the ventromedial prefrontal cortex (vmPFC). However, meth significantly increased metabotropic glutamate receptor-5 (mGluR5) expression in the dorsal hippocampus. Treatment with URB597 increased CB1 and FAAH expression in the dorsomedial prefrontal cortex (dmPFC) and vmPFC, respectively. Taken together, these results implicate the involvement of the eCB system in meth abstinence. However, other eCB-modulating therapeutics should be considered. Our ongoing AEA concentration assessments will be critical in evaluating the potential role of AEA in meth relapse.

Oral Communication 1-2

Histone acetyltransferase KAT2A is a critical mediator of drug-associated learning and transcription in the nucleus accumbens

Emerson, Soren D[1]; Lopez, Alberto J[1]; Bethi, Rishik[1]; Konomi-Pilkati, Ainoa[1]; Adank, Danielle N[1]; Christensen, Brooke A[1]; Leonard, Michael Z[1]; Yoon, Hye jean[1]; Delgado, Julian[1]; Nolan, Suzanne O[1]; Morris, Allison[1]; Johnson Amy R[1]; Rose, Kristie[1] and Calipari, Erin S[3]

[1]Department of Pharmacology, Vanderbilt University, Nashville, TN USA

The onset and maintenance of cocaine use disorder are driven by physiological and transcriptional changes within the brain that lead to maladaptive cocaine taking and seeking; however, the underlying molecular mechanisms remain opaque. Epigenetic mechanisms in which environmental stimuli cause long-lasting changes in gene expression within the brain have recently emerged as a critical driver of drug-induced neuronal adaptations in substance use disorder. We have identified lysine acetyltransferase 2a (KAT2A) as a novel cocaine-recruited epigenetic regulator within the nucleus accumbens (NAc). In vivo, cocaine administration increases the KAT2A-recruiting covalent mark on histone H3 (H3S10P), KAT2A:H3 associations, and KAT2A-associated acetylation of H3 (H3K9Ac), which is permissive to gene expression. Further, we show that manipulation of KAT2A in vivo using systematic pharmacology or in a region- and cell type-specific manner prevents drug-associated learning assessed via cocaine locomotor sensitization and self-administration. Finally, using single-nucleus RNA sequencing, we characterize the influence of KAT2A on the formation of transcriptionally active cell populations following cocaine administration. Together, these results highlight drug-induced recruitment of a novel epigenetic regulator and the role it plays in drug-associated learning, offering a potential future therapeutic target to alleviate the devastating impact of cocaine use disorder on public health.

Oral Communication 1-3

Sex-Dependent Effects of 2,5-Methoxy-4-Iodoamphetamine (DOI) on Methamphetamine Self-Administration: Mechanistic Insights from Antagonism and PET Imaging Studies

Wood, Bo Jarrett[1,3]; Patisaul, Patrick Earl[1,3]; Cannon E Christopher[1,3]; Barnes Miranda[5]; Lokitz, Stephen[5]; Blough, Bruce E[4]; Murnane, Kevin Sean[1,2,3]

[1]Department of Pharmacology, Toxicology, and Neuroscience, LSU Health Shreveport, Shreveport, Louisiana, USA; [4] Center for Drug Discovery, Research Triangle Institute, Research Triangle Park, NC, USA; [5] Center for Molecular Imaging and Therapy, Shreveport, Louisiana, USA

Methamphetamine (MA) is a highly addictive psychostimulant with no FDA-approved treatments, despite its significant public health impact. Psychedelics, 5-HT2A agonists, are gaining clinical attention, yet their potential to attenuate MA reinforcement remains underexplored. This study investigated the effects of the synthetic psychedelic 2,5-methoxy4-iodoamphetamine (DOI) on MA self-administration and 5-HT2A receptor involvement using the antagonist M100907. Male and female Sprague-Dawley rats (N = 8 per sex) were trained to self-administer MA on a fixed ratio 4 schedule of reinforcement. Following stable responding, DOI (0.1 or 0.32 mg/kg) was administered 15 minutes before sessions to assess dose-dependent effects on MA intake. The peak DOI dose was tested across varying MA doses (0.03 and 0.06 mg/kg/infusion) to evaluate shifts in the dose-response curve. To confirm 5-HT2A involvement, M100907 (0.1 mg/kg) was administered prior to the peak DOI dose. Food-maintained rats served as controls to assess behavioral specificity. PET imaging assessed in vivo 5-HT2A receptor occupancy (DOI: 0.1, 0.32, 1 mg/kg). DOI significantly reduced MA intake in males but not females, indicated by a repeated measure 2-way ANOVA, with effects blocked by M100907. DOI more potently suppressed MA self-administration compared to food controls in males. At the peak dose (0.32 mg/kg), DOI achieved ~80% 5- HT2A receptor occupancy in both sexes, despite behavioral differences. These findings suggest 5-HT2A agonists, like DOI, could reduce MA intake, with sex-specific mechanisms warranting further study.

Oral Communication 1-4

Effects of oral hormonal contraceptives on amphetamine-seeking behavior

Vasquez, Adriana[1,2]; Mendoza, Paola J[3]; Kim, Gahyun[1]; Antonacci, Payton E[1]; Dominguez, Juan M[1,2,3,4]; Monfils, Marie-H[1,3], and Lee, Hongjoo J[1,3]

[1]Dep. of Psychology; [2]Waggoner Center for Alcohol & Addiction; [3]Institute for Neuroscience; [4]Dep. of Pharmacology and Toxicology, University of Texas, Austin, TX USA

Evidence suggests that increased levels of gonadal hormones (e.g., estradiol & progesterone) play an important role in the maintenance of female substance use disorders (SUD). A common type of treatment for SUD is exposure therapy—an approach largely based on extinction. Endogenous gonadal hormones have well-documented effects on the hedonic responses to drugs of abuse. However, the influence of their synthetic counterparts, used in hormonal contraceptives (HC), have received little attention, particularly in extinction paradigms. The current experiment investigated whether Levonorgestrel (LNG), synthetic progestin used in HCs, during either extinction and/or reinstatement would attenuate AMPH-preference. To investigate this, naive and untreated female rats first underwent AMPH conditioning during an estrous cycle stage associated with higher levels of gonadal hormones (i.e., proestrus/estrus; P/E). Then, they were tested for their AMPH-preference for three sessions (extinction learning) after receiving either oral administration of LNG or during P/E. Half of the rats from each group discontinued or continued LNG treatment prior to being presented with a challenge dose of AMPH (reinstatement). Results showed that females receiving LNG during extinction displayed decreased AMPH-preference, as compared to females tested in P/E. However, when LNG was discontinued during reinstatement, rats showed robust reinstatement of AMPH-preference while the rats that continued to receive LNG did not show significant reinstatement of AMPH-preference. This suggests that the combination of extinction and HC use are important to attenuate AMPH-preference but are not sufficient to prevent reinstatement if HC use is discontinued. Overall, the findings propose that HCs can be a useful tool, in combination with exposure therapy, to treat SUD in women seeking treatment.

Oral Communication 1-5

Impacts of contraceptive hormone ethinyl estradiol on the primary reinforcing and reinforcer-enhancement effects of nicotine

McNealy, Kathleen R[1], Knabel, MacKenzie L[1], Smyth, Sophia M[1], Reinke, Drake[1], Brester, Ella[1], Gipson, Cassandra D[2], Barrett, Scott T[1], Bevins, Rick A[1]

[1]University of Nebraska-Lincoln, Lincoln, Nebraska, U.S.A, [2]University of Kentucky, Lexington, Kentucky, U.S.A

Hormonal contraceptives are taken by ~50% of premenopausal smokers. Many hormonal contraceptives contain a synthetic estrogen (e.g., ethinyl estradiol/EE). EE heightens nicotine intake. However, whether this heightened consumption reflects alteration in nicotine reinforcement or enhancement by nicotine of co-occurring reinforcers is unknown. This latter reinforcer-enhancement effect is modeled in rats by measuring responding maintained by nicotine alone or nicotine with a reinforcing visual stimulus (VS). We thus examined the effects of EE on nicotine reinforcement and reinforcer-enhancement. Ovary-intact female Sprague-Dawley rats (N=92) were assigned to daily injections of EE (vehicle, 0.125 [Low EE], or 0.18 [High EE] mcg/day) and to self-administer IV infusions of 0.03 or 0.06 mg/kg nicotine or saline during two, ten-session phases. Rats started in an Infusion Only Phase, responding only for their assigned solution on a Variable Ratio (VR)-3 schedule. Rats then progressed to the Infusion+VS Phase where completion of the VR3 resulted in an infusion of their assigned solution plus a 30-second VS. During the Infusion Only Phase, responding maintained by 0.06 but not 0.03 mg/kg/inf nicotine was higher than saline. Thus, only 0.06 mg/kg nicotine evidenced any primary reinforcing effects. This effect was not impacted by EE. For the Infusion+VS Phase, EE altered nicotine-maintained responding. Vehicle rats responded more for 0.03 mg/kg/inf nicotine than saline or 0.06 mg/kg/inf nicotine, whereas Low EE rats responded more for 0.03 and 0.06 mg/kg/inf nicotine than saline. High EE rats did not self-administer any nicotine dose. Thus, EE altered nicotine reinforcer-enhancement but not nicotine primary reinforcement. These results support investigation of novel nicotine cessation therapies for women taking EE-containing contraceptives.

Oral Communication 1-6

AT-1001, a potential therapeutic agent for smoking cessation

Kusi-Boadum, Nana Kofi[1] *, Shetty, Ritu PhD[1], Gatch, Michael PhD[1], Sumien, Nathalie[1] PhD, Forster, Michael PhD[1]

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Purpose: Unlike the α4β2 nicotinic acetylcholine receptor, the α3β4 nicotinic acetylcholine receptor subtype, remains underexplored as a target for smoking cessation therapies. Although studies have shown that α3β4 antagonism attenuates nicotine self-administration and thus reward, they have not separated the central vs peripheral contributions of the α3β4 receptor. AT-1001 is a blood brain barrier-permeable α3β4 nicotinic acetylcholine receptor partial agonist that has been shown to inhibit nicotine reward. Method: Locomotor activity was assessed in Swiss-Webster mice using a standard apparatus to evaluate the independent effects of AT-1001, its antagonistic action on nicotine's biphasic locomotor effects, and the reversal of its independent locomotor effects by hexamethonium. Discriminative stimulus effects of AT-1001 were tested in male Sprague-Dawley rats trained to discriminate nicotine tartrate (0.1 mg/kg, 5-minute pretreatment) from saline. Percentage of drug lever responses and response rate were recorded and analyzed using repeated measures ANOVA. Results: In locomotor activity tests, AT-1001 at doses of 2.5 mg/kg and 5 mg/kg replicated nicotine's initial depressant effect within the 20-40-minute period of the 2- hour study but did not produce a significant later stimulant effect. Hexamethonium did not reverse this depressant effect. In the interaction study, AT-1001 dose-dependently reversed nicotine's latter stimulant effect. In the drug discrimination assay, AT-1001 partially substituted for nicotine's discriminative stimulus effect. Conclusion: The nicotine-like effects of AT-1001 indicate that central α3β4 receptors are crucial in mediating nicotine's overall emotional state. As a partial agonist similar to varenicline, AT-1001's ability to antagonize nicotine's stimulant effect aligns with studies demonstrating its efficacy in attenuating nicotine self-administration. This makes it a promising candidate for smoking cessation.

Oral Communication 2-1

Effects of Chronic Fentanyl Exposure in Squirrel Monkeys

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Fentanyl-related opioid overdose deaths and opioid use disorder (OUD) is a major public health crisis. Previous work has shown that μ-opioid receptor agonists produce tolerance that may be associated with dependence and increased sensitivity to antagonists. In the present studies, the effects of naltrexone on schedule-controlled food-maintained operant performance were examined in squirrel monkeys (n=4) before and during chronic fentanyl treatment (0.32 mg/kg/day; SC). Prechronically, fentanyl (0.0001-0.01 mg/kg, IM) and oxycodone (0.032-0.56 mg/kg, IM) produced a dose-related decrease in responding. In contrast, naltrexone (0.32 mg/kg, IM) had no effect on operant performance compared to control. Chronic redetermination of drug effects revealed a >5-fold rightward shift in the dose-response function for fentanyl and oxycodone. Naltrexone (0.0001-0.0032 mg/kg; IM) produced dose-related decreases in food-maintained behavior. Observation studies (30 min) were conducted to quantify changes in somatic behaviors. Pre-chronic treatment of naltrexone (0.32 mg/kg, IM) did not modify observable behavior from control (total count 21 vs 20.5). Naltrexone (0.0001- 0.0032 mg/kg; IM) during chronic fentanyl produced a dose-dependent increase in distress vocalizations and licking behaviors, with the highest dose inducing 78.5 observable signs compared to control values (22.6). Discontinuation of chronic fentanyl treatment revealed time-dependent increases in low posture and holding of the abdomen behaviors. These data are consistent with the view that chronic fentanyl-induced μ-opioid receptor activation produces tolerance to effects of opioid agonists and enhances sensitivity to behaviorally disruptive effects of antagonists. The increased sensitivity to the effects of naltrexone coupled with the naltrexone-precipitated and fentanyl discontinuation induced emergence of somatic observable signs may be indicative of withdrawal (supported by DA058544-01A1).

Oral Communication 2-2

Relationships between fentanyl self-administration and risk-taking behavior in rats

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Individuals with opioid use disorder display elevated risk-taking behavior. To explore relationships between opioid use and risk taking, our lab employs a rodent model of decision making involving risk of explicit punishment (Risky Decision-making Task; RDT). In Experiment 1, we examined whether individual differences in risk preference in the RDT predicted aspects of self-administration of the synthetic opioid fentanyl. Male and female Sprague-Dawley rats were characterized on the RDT and then underwent fentanyl self-administration (6 hours/day) for 21 days. Rats escalated their fentanyl intake, but neither rate of escalation nor overall fentanyl intake were associated with risk preference. To determine whether chronic opioid use leads to increased risk taking, male and female rats were trained on the RDT until stable behavior emerged and then underwent fentanyl self-administration (6 hours/day) or sucrose self-administration for 14 days. Rats remained undisturbed for 3 weeks and then re-tested on the RDT to assess fentanyl-induced changes in risk taking. Relative to performance before self-administration, rats that self-administered fentanyl displayed increased risk taking. To determine whether this fentanyl-induced increase in risk taking could be attenuated, rats were given systemic injections of the selective dopamine D2 receptor (D2R) agonist sumanirole before being tested on the RDT. Sumanirole decreased risk taking in fentanyl exposed rats, suggesting that D2R activation may be a potential strategy for mitigating opioid-induced increases in risk taking. Future studies will explore the contribution of D2Rs to fentanyl-induced increases in risk taking in regions known to play a role in adaptive risk taking. Collectively, this work will provide important insight into the neurobehavioral mechanisms underlying the relationship between opioid use and altered risk taking.

Oral Communication 2-3

Sex differences in the effects of serotonin-2A activation on fentanyl demand in Sprague-Dawley rats

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Fentanyl abuse and overdose deaths have yet to be ameliorated. Hallucinogenic compounds reduce opioid self-administration, but the extent to which this is driven by the 5-HT2AR is unknown. The 5-HT2AR agonist 25CN-NBOH (25CN) is 100x more selective for the 5-HT2AR than the 5-HT2BR and 5-HT2CR. We hypothesized that pre-treatment with 25CN would reduce fentanyl self-administration. Male (n=16) and female (n=16) Sprague-Dawley rats were trained to self-administer fentanyl in daily 3 hr sessions. After acquisition, rats were transitioned to a within-session threshold procedure where they sampled 11 doses that decreased by ¼ log every 15 minutes. Once stable, rats were pretreated with vehicle or 25CN (0.03, 0.1, 0.3, and 1.0 mg/kg; i.p. within-subjects and counterbalanced). Finally, rats were tested in a cue-induced drug seeking test. An exponentiated demand curve analysis was used to extract Q0 and α, which summarize consumption at near-free prices and resistance to price increase, respectively. Results revealed that male rats under vehicle conditions had increased Q0 and decreased α when compared to female rats, suggesting that males valued fentanyl more than females. Pretreatment with 0.3 and 1 mg/kg doses of 25CN decreased Q0 in both sexes. None of the doses of 25CN affected α. The selective 5- HT2AR antagonist M100907 fully blocked the effects of 25CN on Q0 while the 5-HT2CR antagonist SB242084 did not. 25CN did not reduce cue-induced fentanyl seeking. These results suggest that highly selective 5-HT2AR agonists do not alter the reinforcement value of fentanyl but may enhance the potency in a dose-dependent manner. Together, these results warrant continued investigation into 5-HT2AR agonists for opioid use disorder treatment.

Oral Communication 2-4

Characterizing Sleep Disruptions Associated with Morphine-Dependence and Spontaneous Withdrawal in Rats

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Sleep disturbances during opioid withdrawal are a significant but untreated symptom that contribute to relapse. While several FDA-approved treatments for opioid use disorder (OUD) disrupt sleep in opioid-naive individuals, their effects during withdrawal and extended abstinence remain poorly understood. This study examined the impact of morphine-induced dependence and withdrawal on sleep using a rodent model. Male Sprague-Dawley rats (n=16) were implanted with subcutaneous transmitters and subcranial electrodes for telemetric recording of electroencephalography (EEG) from their home cage. Morphine was administered non-contingently twice daily, at escalating doses (10-40 mg/kg, s.c.) for 4 days, followed by once daily (40 mg/kg) for ~30 days, then 2 weeks of abstinence. EEG was recorded for 24- consecutive hours every 3-5 days and scored for wake, REM, and NREM sleep. Withdrawal peaked at 18-22 hours post-morphine, with significant sleep disruptions starting around day 5, including reduced NREM and REM sleep by ~50%. These disruptions persisted throughout 30 days of withdrawal, returning to baseline after 2 weeks of abstinence. Additionally, 0.1 mg/kg buprenorphine administration during extended withdrawal reduced NREM and REM sleep, similar to the effects in opioid-naive rats. These findings suggest that morphine withdrawal consistently disrupts sleep, and that buprenorphine exacerbates sleep disturbances in both dependent and opioid-naive states, highlighting the need for further research on underlying mechanisms and treatment options.

Oral Communication 2-5

An orally available negative allosteric modulator of mu-opioid receptor precipitated minimum withdrawal symptoms and reversed fentanyl's effects in drug discrimination

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Opioid use disorder (OUD) remains a critical public health challenge, with approximately 1.6 million individuals affected and 10.1 million persons misusing opioids in 2019 alone. Current FDA-approved therapies—methadone, buprenorphine, and naltrexone— target the orthosteric binding site on the mu-opioid receptor (MOR). However, these treatments are associated with significant drawbacks, including addiction liability (methadone and buprenorphine), respiratory depression (methadone), and poor patient compliance due to severe withdrawal symptoms (naltrexone). To address these limitations, we are developing negative allosteric modulators of MOR (mu-NAMs) as a novel therapeutic strategy. These muNAMs target MOR outside the orthosteric binding pocket in a non-surmountable fashion, offering the potential to mitigate opioid misuse. Through a rigorous structure-activity relationship campaign, we identified a novel potent mu-NAM, US007. When tested against an EC80 concentration of DAMGO, in GTPγS binding and β-arrestin recruitment assays, US007 exhibited 50-60 nM potency. US007 (10 and 32 mg/kg, i.p. or p.o.) was able to partially block the action of 32 mg/kg morphine in antinociception assays in mice. In morphine-dependent mice, 32 mg/kg US007 precipitated significantly fewer withdrawal symptoms, including jumps and paw tremors, compared to 1 mg/kg naltrexone. Furthermore, in a rat drug discrimination model, preliminary results showed that 1 mg/kg 698 alleviated the subjective effects of 0.032 mg/kg fentanyl. These results demonstrate this is the first mu-NAM to show promise in preclinical models of OUD, highlighting its potential as an innovative treatment. Funded by R41 DA056254 and the Michigan Economic Development Corp and MTRAC for Life Sciences.

Oral Communication 2-6

Investigating Opioid and Nicotine Effects on Perineuronal Net Structures in Wistar Rats

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The nonmedical use of opioids is a significant health problem, and co-occurring use of opioids and nicotine may exacerbate the risk of developing polysubstance use disorder/dependence. Specialized extracellular matrix proteins, perineuronal nets (PNNs) are implicated in plasticity and drug-related conditioning. We hypothesized that tolerance to repeatedly administered oxycodone, fentanyl, and/or nicotine would modulate expression of PNNs. Male or Female Wistar rats (~10 weeks old) were randomly assigned to groups that received acute or repeated injections (twice daily for 7 days) of oxycodone (2-4 mg/kg, i.p.), fentanyl (4-125 µg/kg, s.c.), nicotine (0.4-2 mg/kg, s.c.) or 0.9% saline vehicle. Thermal antinociception (i.e. tail withdrawal test) was used to validate acute drug intoxication and tolerance. A separate cohort of male rats were trained to self-administer intravenous fentanyl (0.625-10 µg/kg/inf) during 8-hour sessions. Serial collection of whole-brain coronal slices and immunohistochemistry were used to identify Wisteria Floribunda Agglutinin (WFA)-positive perineuronal net structures in cortical brain regions. Oxycodone, fentanyl, and nicotine injections produced significant antinociception (increased latency in the tail withdrawal test), as well as tolerance following repeated injection ($p < 0.05$). Changes in PNN density and intensity were observed in the orbitofrontal cortex (OFC) in a duration-dependent manner following repeat opioid and nicotine administration relative to controls ($p<0.05$), but not following escalation of fentanyl self-administration. Analyses confirmed a significant correlation between PNN intensity and magnitude of behavioral tolerance. Overall, these data confirm that opioid and nicotine administration and abstinence in rats may alter extracellular matrix structures integral to neuroplasticity-related learning and memory. This may indicate a key mechanism underlying the role of PNNs in tolerance and polydrug-use vulnerability.

Oral Communication 3-1

Substance use and SIV infection in macaques ameliorate a cerebrospinal fluid single-cell transcriptomic profile associated with neurocognitive impairment

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More than 50% of the people living with HIV (PLWH) experience HIV-associated neurocognitive disorders (HAND), which get exacerbated by comorbid conditions like opioid use disorders. We utilized a well-characterized rhesus macaque model of SIVmac251 treated with a combination of antiretrovirals (cART) and morphine regimen. The CSF scRNA-Seq was performed longitudinally on pooled CSF cells to profile cell-specific transcriptomic signatures. We observed a higher percentage of the MSR1+(CD204) microglia-like cells within the monocyte populations from morphine-treated macaques than controls. Cell type-specific differential gene expression analysis revealed dysregulation of antiviral gene response pathways, pathways involved in cellular responses to misfolded proteins, within the monocyte subsets in morphine-treated macaques. Further, cell-cell receptor-ligand interaction revealed an altered number of inter-cellular interactions, for the CD14+ monocyte populations, the intra/inter-cell communication involving ligand-receptor pairs, including APOE-TREM2, APP-(TREM2+TYROBP), APP-CD74, SPP1–(ITGA4+ITGB1), were significantly dysregulated in the morphine group. These findings indicate that opioid-mediated dysregulation of antiviral response and energy metabolism signaling in CSF monocytes may be responsible for higher seeding and persistence of SIV reservoirs in CNS. Additionally, we identified opioid-mediated altered cell-specific transcriptomic signatures and cell-cell communication pathways associated with the development of neurocognitive impairments in PLWH.

Oral Communication 3-2

Diurnal variation in striatal acetylcholine release and Pavlovian behavior

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Mesolimbic reward circuitry contributes to individual differences in SUD risk, and examining the behavioral implications of diurnal rhythms in this circuitry may provide insight into SUD pathophysiology. Cue-directed Pavlovian conditioned behavior, or "sign-tracking (ST)," is associated with increased drug self-administration and represents a potential analogue for SUD risk. Induction of ST depends on dopamine (DA) bursts in the nucleus accumbens (NAc), which are facilitated by pauses in the constituent activity of local cholinergic interneurons (CINs). Previous findings indicate that DA burst magnitude and rates of ST are increased in the dark period of a 12-hour light/dark cycle, and reduced CIN activity may underlie this diurnal increase. Reward devaluation, a model of habit-like behavior, may be mechanistically related to ST and SUD risk. To test the hypotheses that reward devaluation covaries diurnally with ST and that promoting striatal CIN activity abolishes diurnal rhythms in these behaviors, we used Cre-dependent excitatory DREADDs to manipulate NAc CIN firing in male transgenic Cre-expressing rats (N=9) and their Cre-negative littermates (N=10). Subjects underwent sucrose-rewarded Pavlovian conditioning, and we used a within-subjects design to compare 7 testing sessions with DREADDs activated by designer drug injection to 7 subsequent sessions with only a saline injection. Two final saline sessions were then completed with the addition of a reward devaluation manipulation in which subjects were offered ad-libidum sucrose reward prior to testing. Animals completed the entire experiment in either the light (N=8) or dark (N=11) period. Consistent with previous findings, rates of ST were higher during the dark cycle and additionally, we found that DREADD-mediated CIN excitation abolished diurnal differences in responding. Interestingly, while outcome devaluation was negatively related to ST in the dark period, responding was readily devalued in the light period. These findings support the theory that diurnal variation in reward-related behaviors, but not habit-like behaviors, are mediated by striatal CINs.

Oral Communication 3-3

Chronic exposure to arsenobetaine in mice is associated with cognitive impairments and changes in brain gene expression

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Arsenic exposure is a significant public health concern. We have found that arsenobetaine (AsB), an organoarsenic species, bioaccumulates in the brain. We hypothesize that exposure to AsB during early development affects the brain and may contribute to neurodevelopmental disorders. We investigated the effects of chronic AsB exposure on behaviors associated with anxiety as well as learning and memory and gene expression changes in the brain of J:ARC male and female mice. Mice received either 1000 ppb AsB in water or water alone from weaning. At P70-80, animals were tested in the light-dark box, elevated plus-maze, and the water T-maze. Animals were euthanized at P83, brains were harvested, and the amygdala, prefrontal cortex, and hippocampus were dissected for RNA sequencing to assess gene expression. Animals exposed to AsB displayed higher levels of anxiety and cognitive impairment, with the effects of AsB on anxiety behaviors being more prominent in females. Differential gene expression analysis revealed global changes in gene expression following AsB exposure, with the amygdala being more affected in females, while the hippocampus being more affected in males. Several genes implicated in synaptic plasticity and regulation of fear/anxiety (e.g., Crh, Drd1) as well as learning and memory (e.g., Ppp1r1b, Egr1) were downregulated by AsB exposure. Cell type enrichment analysis of differentially expressed genes suggested that neurons in the female amygdala and male dentate gyrus were vulnerable to arsenic exposure. These findings suggest that chronic AsB exposure affects brain processes in a sex- and region-specific manner, indicating potential long-term neurological risks.

Oral Communication 3-4

Investigating how chronic stress exposure in rats sex-specifically affects willingness to work for sweet + salty reinforcers and overall home cage salt consumption

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People broadly consume more salt (NaCl) than physiologically needed. Like reinforcing drugs, chronic stress exposure can increase the intake of palatable foods. While most studies have evaluated how high sucrose/fat diets influence rodent behavior, how chronic stress and high salt diet interact to affect behavior haven't been studied. Salt studies rarely assess female rodents, nor salt intake's impact on operant behaviors (i.e., lever-pressing). Thus, we are sex-specifically assessing how home cage access to salty food affects work effort for salty + sweet (4% NaCl + 31% sucrose) reinforcers before, during, and after chronic stress exposure. Previous work shows male rodents voluntarily consume more palatable foods than females, so we hypothesized males on high salt diet would work harder for salty + sweet reinforcers, and chronic stress would increase salty food intake across sex. Adult (>9wks) female (n=14) and male (n=12) rats were assigned to high (4.0%, w/w) or low (0.4%) salt diets, or given free access to both (mixed), in their home cages and trained to lever press for salty + sweet reinforcers. After a 4wk baseline, rats were exposed to 2 stressors weekly for 4wks, followed by 4wks of no stress exposure. We evaluated data using two-way repeated measures ANOVAs, and pairwise comparisons with Bonferroni correction. Preliminary findings indicate females on mixed diets willingly consume more high salt than males. While chronic stress exposure isn't showing any effects, there is a non-significant trend indicating females may work harder for reinforcers than males. Seeking salt independent of stress suggests it is reinforcing even in salt-replete mammals. In fact, intake of salt and drugs are both regulated by opioid receptors in the brain's incentive salience network. Future studies should investigate how high salt affects willingness to work for reinforcing drugs, and how chronic stress exposure may indirectly influence drug-seeking.

Oral Communication 3-5

Insulin-like growth factor 1 and its receptor in prefrontal cortex regulates heroin addiction-induced behavioral and synaptic plasticity

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Opioid use disorder (OUD) is a chronic, relapsing mental illness characterized by compulsive drug seeking and vulnerability to relapse. Clinical studies show that the neuronal responses to stimuli in the prefrontal cortex (PFC) from individuals with OUD are disrupted. Consistently, preclinical data also report opioid-induced synaptic dysfunction in the PFC. Given the critical role of PFC in regulating opioid-related behaviors, it is vital to investigate the molecular mechanisms underlying opioid-induced PFC dysfunction and its role in shaping opioid-induced behavioral plasticity. Increasing studies have shown that insulin-like growth factor 1 (IGF1) and IGF1 receptor (IGF1R) regulate synaptic transmission, but the involvement of IGF1/IGF1R in opioid addiction-induced synaptic deficits remains unknown. Here we used a mouse heroin self-administration (SA) model to investigate the role of IGF1/IGF1R on heroin-induced behavioral, synaptic and transcriptional plasticity. We found that IGF1/IGF1R and its downstream signaling in PFC were reduced after prolonged abstinence from heroin SA. Intra-PFC IGF1 administration attenuated while IGF1R selective knockdown in PFC pyramidal neurons potentiated heroin-seeking behavior, heroin motivation and dose response. Intra-PFC IGF1 administration restored the decrease in excitatory neurotransmission caused by prolonged abstinence from heroin SA and recovered the PFC neural activity both in-vivo and in-vitro. Lastly, IGF1 treatment also restored a large set of genes involved in neural signaling in PFC of heroin SA mice after prolonged abstinence. These data indicate that IGF1/IGF1R system in the PFC plays a key role in regulating heroin-induced behavioral, synaptic and transcriptional plasticity, which will provide a novel therapeutic target for the development of OUD treatment strategies.

Oral Communication 3-6

The effects of cocaine delivery rate on drug-conditioned behavior and neural dynamics in the nucleus accumbens

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The rate of cocaine delivery dramatically influences its acute reinforcing effects, and is a key determinant for the risk of developing cocaine use disorder. In preclinical models, animals preferentially respond to receive fast drug infusions over slower administration of the same dose. Rapid cocaine infusions also selectively potentiate plasticity markers within the striatum, despite producing comparable peak drug concentrations. It remains unclear how the temporal dynamics of cocaine's actions in the striatum mediate differential neurobehavioral outcomes. The current studies employ in vivo microendoscopic imaging (i.e. miniscope) in freely moving mice to monitor multiple indicators of neural activity within the nucleus accumbens (NAc) across modes of cocaine administration. To address how the rate (3, 30, 100s; 3.0mg/kg) of IV drug administration influence patterns of activity within the NAc, mice (n=18) expressing the genetically-encoded calcium sensor GCaMP8 were implanted with a gradient-index (GRIN) lens for microendoscopy. We find that cocaine has reproducible effects on cellular activity within the NAc – increasing the activity of a small population of neurons, while robustly decreasing activity in the majority of remaining cells. While this general pattern was observed across all conditions, the time-course and number of cells that were sensitive to cocaine's effects were dynamically modulated by injection speed. Over repeated exposure, a subset of cocaine responsive cells was more likely to be active at the onset of drug infusion, suggesting a potential conditioned component that may further influence cocaine's pharmacodynamic actions in the NAc. Collectively, these studies characterize how cocaine pharmacokinetics differentially influence neural dynamics within striatal circuitry – which may contribute to the acute reinforcing properties of cocaine and, perhaps, its long-term behavioral consequences.

Oral Communication 4-1

In vivo and in vitro drug-drug interactions between synthetic cannabinoid receptor agonists and psychiatric drugs

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Individuals with certain mental health conditions are susceptible to substance use disorders, and are likely to co-administer prescribed medications and drugs of abuse, leading to adverse outcomes. Clinical and pathological reports indicate the simultaneous presence of specific therapeutic + illicit drug pairs, including Xanax (alprazolam) + synthetic cannabinoid receptor agonist (SCRA) 5F-APINACA, and Prozac (fluoxetine) + JWH-018 in blood. Both drug pairs undergo metabolism by CYP3A or CYP1A enzymes, respectively, and thus, we hypothesized that the therapeutics inhibit SCRA metabolism, increasing cannabinoid levels and leading to prolonged in vivo effects. In male and female C57BL/6 mice, both SCRAs elicited dose-dependent hypothermic effects. Hypothermic effects of 5F-APINACA lasted longer in the presence of alprazolam, but not lorazepam, a positive pharmacodynamic and negative pharmacokinetic control. Likewise, hypothermic effects of JWH-018 were extended in the presence of fluoxetine, but not in the presence of its control SSRI citalopram. Subsequent in vitro mechanistic kinetic studies with C57BL/6 mice liver microsomes showed that alprazolam was a moderate mixed inhibitor toward the hydroxylation of the 5F-APINACA adamantyl group. Ex-vivo studies on the abundance of CYP450 enzymes following chronic administration of fluoxetine and alprazolam were further done, with data to be presented. These observations are consistent with therapeutics and SCRAs competing for common CYP metabolic pathways to suppress metabolism and prolong in vivo effects in mice. Taken together, these findings highlight the potential for interactions between prescription medications and synthetic cannabinoids.

Oral Communication 4-2

Prenatal alcohol and cannabinoid exposures impose distinct, sex-specific epigenetic signatures of alcohol-seeking behaviors in adult mice

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Background: Individuals with prenatal exposure to alcohol or marijuana are at greater risk of developing alcohol use disorder, which can be associated with dysregulated striatal synaptic activity. We investigated whether simultaneous alcohol and cannabinoid exposure (SAC) augments alcohol-seeking in offspring, and whether behavioral changes are associated with changes in cannabinoid receptor 1 (CNR1) gene networks. Methods: Pregnant C57Bl/6J mice were assigned to one of four groups: drug-free control, alcohol-exposed, cannabinoid-exposed, or SAC-exposed. From Gestational Days 12-15, dams received cannabinoid agonist CP-55940 (750µg/kg) or saline via intraperitoneal injection. Dams were placed in vapor chambers for 30 minutes of inhalation of 95% ethanol or room air. Adult offspring (Postnatal Days 120+) were assessed for alcohol-seeking activity within operant chambers. Approximately one year after birth, offspring Dorsal Striatum (DS) tissues were collected for bulk RNA-sequencing and transcript quantification of preselected CNR1-associated genes. Results: In females, all forms of prenatal exposure increased alcohol consumption under fixed and progressive-ratio (PR) paradigms. In males, polysubstance exposure increased alcohol consumption under PR schedules and alcohol-seeking during acute abstinence. Prenatal SAC further imposed a persistent decrease in CNR1 receptor-interacting protein (CNRip1), without affecting CNR1 expression. As CNRip1 negatively regulates presynaptic CNR1 activity, SAC exposure may result in hyperactive CNR1 signaling. Furthermore, SAC exposure appears to increase gene expression associated with synaptic formation and disrupt relationships between synaptic DS gene expression and alcohol-seeking behaviors. Conclusion: Prenatal SAC exposure imposes distinct, sex-specific behavioral phenotypes of alcohol-seeking and CNR1-associated striatal gene expression compared to single drug exposure, with changes detectable into middle age/adulthood

Oral Communication 4-3

Cognitive effects of chronic ethanol drinking in male and female monkeys.

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Alcohol is one of the most widely used substances throughout the US, contributing to countless health issues including deficits in executive function, particularly cognitive flexibility-the ability to adapt to a change in reinforcement contingencies. These deficits decrease the seeking and compliance of treatment for alcohol use disorder (AUD), leading to a cycle of reduced executive function and continued heavy drinking, further worsening cognitive functioning. The time course and amount of drinking needed to produce these deficits are relatively unknown and difficult to study in humans but can be addressed using animal models due to experimenter control over variables. Our laboratory utilizes a longitudinal model of AUD in nonhuman primates (NHPs) that generates individualized drinking patterns and histories, making it an ideal translational model to study cognitive changes starting from alcohol-naïve and continuing through long-term alcohol drinking. 12 adult cynomolgus monkeys (6/sex) were trained to perform two cognitive tasks on cage-mounted touchscreens: stimulus discrimination, stimulus discrimination reversal (SD-SDR) and a psychomotor vigilance task (PVT). These tasks measure cognitive flexibility and attention, respectively. The primary dependent variables are the number of reversals completed (SD-SDR) and the titrated stimulus duration (PVT). Following acquisition of baseline data, NHPs had open access to ethanol (EtOH) and water 22 hours/day, 5 days/week. After 6 months, cognitive performance was reassessed. No significant effect of sex or time was found in any cognitive measure. A regression on total EtOH intake and percent change in reversals approached significance ($p=0.083$), but total EtOH intake and percent change in titrated stimulus duration showed no significance ($p=0.17$). 6 months of open-access drinking did not produce significant cognitive deficits, suggesting greater EtOH intake is required. Regressions trended toward significance, and further cognitive testing at later time points will help elucidate this relationship. Funding: AA027556

Oral Communication 4-4

Molecular mechanisms underlying TLR7-induced increases in voluntary alcohol consumption in C57BL/6J mice

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Alcohol drinking leads to an activation in the innate immune system causing a neuroinflammatory response. We hypothesize that neuroinflammation induces a positive feedback loop resulting in increased alcohol consumption. The toll-like receptor 7 (TLR7) is an endosomal receptor that induces the expression of proinflammatory cytokines. Chronic activation of TLR7 by the endogenous synthetic agonist R848 leads to escalated ethanol consumption and preference. However, the molecular mechanism is poorly understood. In this study, C57BL/6J mice were treated with i.p. injections of R848 in an every-other day schedule for 20 days. After 10 days of no treatment, the animals were sacrificed for single nucleus RNASeq in the prefrontal cortex (PFC) and the amygdala (AMG) (snRNA-Seq) as well as for Xenium spatial transcriptomics (ST). The snRNA-Seq data revealed more differentially expressed genes (DEGs) in the AMG compared to PFC. DEGs in both brain regions were mainly detected in inhibitory and excitatory neurons. Among glial cells, AMG astrocytes had the most DEGs while in the PFC glial cells seemed to be affected equally. In AMG astrocytes, we identified multiple DEGs involved in blood-brain barrier (BBB)-regulatory mechanisms. This finding is supported by Xenium ST where AMG-containing slices validate the expression pattern of these BBB-associated DEGs in astrocytes of the AMG as well as adjacent brain regions. Furthermore, BBB-regulatory genes have been found to be altered across other cell types in both brain regions with a particular emphasis on the BBB-regulating Wnt signaling. Our data suggests that chronic TLR7 activation via R848 initiates neuroinflammatory processes that induce long-term BBB dysfunction in both a cell type-specific and nonspecific manner. These transcriptome alterations may underlie escalated alcohol consumption.

Oral Communication 4-5

Engagement in non-drug activities is inversely related with alcohol demand

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Drug use is inversely related with the availability of alternative, non-drug reinforcers. A recent study demonstrated that measures of past month non-drug reinforcement (availability, enjoyability, engagement) were associated with return to drug use and life satisfaction among people in substance use treatment. The current study sought to extend those findings to a general population and to determine whether non-drug reinforcement measures were associated with behavioral economic demand. Participants reporting recent alcohol use were recruited using crowdsourcing methods (n = 380) and were asked the average number of hours spent per week doing activities with or without drug use for the past 30 days as well as for the 30 days during their period of heaviest use. A relative frequency score was generated (R-Ratio; drug-related activity / (drug-related + non-drug-related activities)) such that higher values indicated a larger portion of drug-related reinforcement. Participants also completed measures of non-drug enjoyability and availability. Alcohol demand was collected using hypothetical purchase tasks. The degree to which participants rated enjoying and being able to find non-drug reinforcement was inversely related to R-Ratio (p's < 0.001). Curve-derived demand measures were significantly associated with R-Ratio, with larger R-Ratios (i.e., more proportional drug reinforcement) being associated with higher demand intensity (Q0) as well as reduced elasticity (alpha; lower price sensitivity) (p's < 0.001). Further, higher R-Ratios were associated with more drinks per week and a greater number of alcohol use disorder criteria (p's < 0.001). These findings further emphasize the inverse relationship between drug use and the availability, enjoyment, and engagement with non-drug activities, thus highlighting the importance of identifying, considering, and focusing on non-drug targets within the context of developing novel behavioral or pharmacological interventions for substance use disorder.

Oral Communication 4-6

Highly efficacious synthetic cannabinoid receptor agonists containing l-tert-leucinate and an antidote approach against them

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SCRA abuse has risen globally with its emergence in the late 2000s. It exhibits serious adverse effects including hallucinations, cardiovascular abnormalities, coma, or even death. Most SCRAs have an aminoalkylindole/indazole scaffold that is distinct from Δ9- tetrahydrocannabinol (Δ9-THC) found in cannabis. Compared to Δ9-THC, SCRAs demonstrate much higher efficacy and potency at the cannabinoid CB1 receptor (CB1R). Many SCRAs with a specific head group exhibit a maximal efficacy exceeding full agonists, often termed "*superagonism*," which likely elicits a high incidence of adverse/toxic effects. We examined a series of currently bused SCRAs with varying head (l-tert-leucinate vs. l-valinate), core (indole vs. indazole), and tail (5-fluoropentyl vs. 4-fluorobenzyl) moieties to investigate the structure-activity relationship in a series of bioluminescence resonance energy transfer (BRET) assays and confirmed their *superagonism*. With molecular dynamics simulations and mutational approach, the molecular determinants of *superagonism* were studied. Finally, we performed electrophysiological experiments in hippocampal brain slices to determine effects of these SCRAs on glutamate release inhibition mediated by CB1R. CB1R antagonists have the potential to be effective therapeutics for the acute adverse effects of SCRAs. To that end, we have investigated various CB1R antagonists with varying degrees of inhibition efficacy and reversibility provided by the Makriyannis lab, on the highly efficacious/potent SCRAs. The results from BRET and brain slice electrophysiology demonstrate the versatility of different classes of antagonists against SCRAs. Our work characterizes the molecular mechanisms of *superagonism* by SCRAs at CB1R and the reversal of their effects by various antagonists that may reveal a class of antagonists potentially suited for the acute treatment of SCRA abuse.

Poster Presentations

Poster 1

Neurobehavioral Correlates of Dopamine Agonist-Induced Eye-Blinking in the Marmoset

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Dopaminergic dysfunction is implicated in substance use disorders (SUD) and other neuropsychiatric illness, making its characterization essential for understanding the mechanisms associated with these disorders. Eye-blinking serves as a reliable, non-invasive marker of dopaminergic activity. This study investigated how D1-selective (0.03-0.3 mg/kg SKF-82958), D2-selective (0.0001-0.001 mg/kg quinelorane), and nonselective (1.0-5.0 mg/kg cocaine) dopamine receptor agonists modulate eye-blinking in the common marmoset (Callithrix jacchus). In addition, pharmacological modulation of brain functional connectivity (FC) from the putamen, a dopamine-rich brain region, was examined using functional magnetic resonance imaging (fMRI). SKF-82958 led to a dose-dependent increase in blink rates, with the highest dose tested producing >9-fold increase in blinking compared to baseline levels, producing a decrease in putamen FC with somatosensory and parietal areas (PE), while increasing FC with caudate. Highest dose of quinelorane reduced blink rates by approximately 70%, highlighting D2 receptors' inhibitory influence on motor circuits, and time-dependently decreased putamen FC with striatal, somatosensory, parietal, and temporal regions. Cocaine showed only a transient effect, with blink rates decreasing by approximately 20% within the first 20 minutes at the highest dose before stabilizing near control levels. Consistent with previous reports, cocaine selectively increased putamen FC within striatal regions. The present findings align with similar outcomes observed across species, bolstering the relevance of eye-blinking + fMRI as cross-species indicators of dopaminergic function. This study highlights potential applications in characterizing and monitoring neuropsychiatric disorders such as Parkinson's disease, schizophrenia, depression, and SUD, where dopaminergic dysregulation affects motor behavior. Overall, these findings provide additional support for eye-blinking as a non-invasive tool for advancing research in neuropsychiatric disorders.

Poster 2

The glucocorticoid receptor antagonist miricorilant decreases alcohol self-administration in alcohol dependent female rats

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Alcohol use disorder (AUD) is associated with the dysregulation of brain stress and reward systems. The nonselective glucocorticoid receptor (GR) mifepristone has previously been shown to reduce alcohol consumption in alcohol-dependent male rats and in humans with AUD. However, mifepristone's action on progesterone receptors may have undesired effects; thus, testing the efficacy of selective GR antagonists in alcohol drinking is critical. Miricorilant has shown efficacy in decreasing alcohol drinking in alcohol dependent and nondependent male rats and is currently under investigation for the treatment of AUD in humans. Whether miricorilant modulates alcohol drinking in alcohol-dependent and nondependent female rats remains to be determined. We tested the effects of miricorilant on alcohol-related behaviors in female Wistar rats using our chronic intermittent alcohol vapor exposure model of alcohol dependence. Alcohol dependent rats escalated alcohol intake, whereas nondependent rats exhibited stable drinking. Intraperitoneally injected miricorilant dose-dependently reduced alcohol self-administration, with an increased effect in dependent compared with nondependent rats. These findings indicate miricorilant as a potential treatment for AUD.

Poster 3

The Nigro-Thalamic Pathway Modulates Heroin-Driven Behaviors

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The neurobiology of opioid-driven behaviors is not fully understood. Previously, opioid reward has been thought to be mediated by the disinhibition of dopaminergic neurons in the ventral tegmental area. But, more recent research has shown that GABAergic neurons in the substantia nigra pars reticulata (SNr) also play an important role in drug taking and seeking. The current study investigated if a subset of these GABAergic neurons projecting to the ventromedial nucleus of the thalamus (vmThal) play a role in heroin-driven behaviors such as 1) acquisition of conditioned place preference (CPP), 2) intravenous drug self-administration (IVSA), and 3) cue-induced reinstatement of heroin seeking. To do so, we used a chemogenetic approach along with various behavioral paradigms in rats. Chemogenetic excitation of SN-Thal neurons (presumably GABAergic) produced no significant changes in the acquisition of CPP but attenuated reinstatement of heroin seeking and heroin self-administration. These findings suggest that the GABA neurons projecting from the SNr to the vmThal play an important role in heroin self-administration and relapse, but some other pathways most likely control the acquisition of drug reward-related learning.

Poster 4

Investigating sex differences in the motivational consequences of opioid withdrawal using conditioned place aversion paradigm in rats

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Opioid Use Disorder (OUD) is characterized by compulsive opioid drug use, withdrawal, and relapse cycles. Withdrawal symptoms, both somatic and affective, are aversive and can lead to cue associations. While past research indicate women exhibit greater cue-reactivity, studies on sex differences in opioid addiction are limited, mainly focusing on males. Thus, the objective of the present study was to investigate sex differences in the motivational consequences of opioid withdrawal using a conditioned place aversion paradigm (CPA). Intact male and female rats underwent four-day conditioning cycles with morphine pretreatment followed by naloxone-precipitated withdrawal. Results show both groups developed CPA, indicating no significant sex differences. The idea of convergent sex differences suggests that males and females may exhibit the same behavior, however the underlying processes that mediate the behavior could be different. Therefore, we stained sections of brain tissue from the animals above for c-Fos using a standard immunohistochemistry protocol. Quantification of activated cells (c-Fos positive) revealed that male rats had higher c-Fos positive cells in the infralimbic cortex, nucleus accumbens core and shell compared to the females ($p < 0.05$), whereas females had significantly higher c-Fos positive cells in the ventral tegmental area. The data produced here indicates that the infralimbic to nucleus accumbens shell pathway is more active than the prelimbic to nucleus accumbens core pathway in males than in females, suggesting that males may be more prone to making stronger associations to aversive conditions. Because this pathway was not active in females, perhaps there is a different pathway that moderates aversion in females.

Poster 5

Examining adolescent nicotine exposure effects on alcohol intake in a heritable model of psychosis

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Increases in dopamine D2 receptor sensitivity is common in psychosis, including schizophrenia (SZ). People living with SZ often exhibit comorbid substance use disorders with both nicotine and alcohol. Our laboratory has established that rats administered neonatal quinpirole (NQ), a dopamine (DA) D2-like receptor agonist (1 mg/kg), permanently increases DAD2 receptor sensitivity throughout the animal's lifetime. We have recently reported that F1 generation offspring of NQ-treated rats also demonstrate increased DAD2 receptor sensitivity, establishing a heritable model. The combination of adolescent nicotine exposure on the drinking of ethanol (EtOH) was analyzed. During adolescence exposure (P28-48), male and female Sprague-Dawley rats were given a two-bottle choice (2BC) test with water and water with 10% ethanol for 24 h daily. Additionally, rats were administered intraperitoneal (IP) nicotine (0.6 mg/kg, base) 3, 6, and 24 h before EtOH was available. Following 21 d of ethanol/nicotine exposure, drug administration was ceased and locomotor activity was recorded as a measurement of withdrawal. To measure the effects of nicotine-mediated alcohol consumption in adolescence on adult rats, a 2BC test was conducted during adulthood (P63-76). Significant acute EtOH drinking enhancement following nicotine administration was observed at the 3 and 6 h time points marks for F1 generation offspring of NQ-treated rats (QQ) from P34-45. In addition, there were significant increases from day 1 of adult exposure, demonstrating incubation. QQ females exposed to nicotine/EtOH showed a lack of habituation and hyperactivity compared to all other groups. Nucleus accumbens and amygdala dynorphin levels will be measured (data will be presented); oxidative stress will be assessed in both trunk blood and centrally with brain tissue. These findings suggest that adolescent exposure to nicotine and ethanol can have long-lasting effects on ethanol consumption.

Poster 6

Lateral entorhinal cortex encodes cue-reward memories

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Associative memory encoding of cues associated with rewards is critical to motivated behavior, such as the seeking of natural rewards and drug rewards. The lateral entorhinal cortex (LEC) is a brain region critical for associative memory and sends projections to the nucleus accumbens (NAc), a region important in reward. However, whether LEC, including LEC->NAc projection neurons, mediates cue-reward associations is unclear. To address this question, we tested whether sucrose-associated cues activate LEC->NAc neurons in a mouse model of cue-induced reinstatement of food seeking. Mice received stereotaxic injections of retrograde viral vector (AAVrg-syn1-GFP) into NAc to express GFP in LEC->NAc neurons. Mice were trained to self-administer sucrose rewards associated with cues for 14 days, followed by 14 days of extinction, and a cue-induced reinstatement test (Cues; n=8). Controls were left in their homecage during reinstatement (No Test; n=7) or no cues were presented during reinstatement (No Cues; n=8). LEC tissue was taken 90 min after reinstatement and processed for c-fos immunohistochemistry, a marker of neuronal activation. Cue-induced reinstatement of sucrose seeking increased c-fos cell counts in LECs compared to home cage controls indicating that reward cues activate the LEC. These findings suggest that cue-associated memory underlying sucrose seeking is linked to LEC, implicating its role in the regulation of motivated behavior, and may implicate the LEC in disorders of reward, such as substance use disorders and depression.

Poster 7

Discovery of Novel Positive Allosteric Modulators of 5-HT2C Receptor

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Substance use disorder (SUD) contributes to a major health problem in the United States (US). In 2023, it was estimated that 42 million people had used cocaine at some point in their life in the US. Drug overdose has become a leading cause of mortality contributing to 104,000 deaths of people under 45 years old in the US annually. There are no FDA-approved drugs available for SUD, and the available psychosocial interventions have varied and often poor overall effect. Medication assistant therapy is critically needed for cocaine used disorder (CUD). Hypofunctional signaling of 5-HT2C receptor (5-HT2CR) is involved in neurobehavioral processes leading to relapse vulnerability in CUD. Targeting 5-HT2CR to attenuate the CUD relapse is a promising strategy; however, achieving ligand selectivity for 5-HT2CR over 5-HT2AR and 5-HT2BR is challenging due to similarity of their orthosteric binding sites. To attain the selectivity, we are targeting positive allosteric modulators (PAMs) for the 5-HT2CR owing to high sequence dissimilarity across the receptor subtypes. We have identified first-generation 5-HT2CR PAMs (CYD-1-79, CTW0415), which potentiate 5-HT2CR, but not 5-HT2AR or 5-HT2BR signaling in vitro without intrinsic activity. As a proof-of-concept, CYD-1-79 and CTW0415 potentiated in vivo effects as a full 5-HT2CR agonist in male rats, outcome blocked by a selective 5-HT2CR antagonist, validating the dependance on 5-HT2CR function. Additionally, CYD-1-79 suppressed cocaine-seeking in a relapse-like behavioral model in male rats. We are working toward the development of next-generation 5-HT2CR PAMs based on CTW0508 and CTW0456 as the advanced chemical leads to elucidate allosteric pharmacology in vitro and evaluate their 5-HT2CR-linked phenotypes and efficacy in rodent preclinical models of CUD.

Poster 8

Gabapentin Partially Attenuates Morphine Withdrawal in Male Rats

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Gabapentin is widely used off label to treat opioid withdrawal, with anecdotal reports suggesting it attenuates withdrawal symptoms. However, the effectiveness of gabapentin in mitigating opioid withdrawal signs has not been rigorously examined. This study assessed the ability of gabapentin to attenuate the expression of morphine withdrawal in male rats. Morphine dependence was established by administering escalating doses of morphine (10-40 mg/kg) b.i.d. (Days 1-4). Dependence was maintained with 40 mg/kg morphine immediately after daily operant experiments. In 6 rats trained to lever press for sucrose pellets (fixed-ratio 5 schedule) morphine withdrawal was assessed by changes in rate of responding. Saline or gabapentin (3.2-320 mg/kg) was acutely administered 5 min before sessions. In a separate experiment, 7 groups of rats (N=8/group) were used to assess 14 somatic withdrawal signs. Morphine dependence was similarly established in Groups A-D, while Groups E-G received saline. Subsequently, Group A, the morphine-dependent control group, received saline injections, and groups B-G received gabapentin (32, 100, or 320 mg/kg). Rotarod performance was also measured. During morphine withdrawal, food-maintained responding decreased to 15% of nondependent control, and the decrease was partially reversed by acutely administered gabapentin (10-320 mg/kg) to approximately 30% of non-dependent control. No dose of gabapentin altered body weight loss. The 32 mg/kg dose of gabapentin attenuated the number of withdrawal signs (e.g., diarrhea and vocalization) from 9 to 3 and from 3 to 0 on days 1 and 2, respectively. However, attenuation of withdrawal signs did not appear to be due to nonspecific behavioral disruption because 32 mg/kg gabapentin did not decrease rotarod performance. These results highlight the need for further research into the effectiveness of gabapentin in managing opioid withdrawal, given its widespread use for this purpose. Supported by USPHS grants R01DA058018 (TH) and R25DK113659 (the STEP-UP HS program; IXD), and the Welch Foundation (Grant AQ-0039; CPF).

Poster 9

Evaluating the locomotor and discriminative stimulus effects of fluorinated analogs of amphetamine and methamphetamine.

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The prevalence of fluorinated amphetamine and methamphetamine analogs on the illicit drug market has continued to increase in recent years. These 'designer drugs' remain popular among drug users; bypassing legal regulations while providing reinforcing effects comparable to cocaine, 3,4-methylenedioxymethamphetamine, amphetamine and methamphetamine. However, their usage has been associated with significant adverse effects including cerebral hemorrhage, heart failure and death—representing a danger to public health. The present study sought to investigate the in vivo pharmacology and abuse potential of five synthetic stimulant compounds: 2- and 3-fluoroamphetamine and 2-, 3- and 4-fluoromethamphetamine. The open-field assay was used to observe locomotor stimulant/depressant effects and evaluate effective dose ranges and time courses for psychoactive effects in groups of 8 male Swiss-Webster mice, (N=192). Male Sprague-Dawley rats (N=48) were trained to discriminate methamphetamine from saline using a FR 10 for food reinforcement in a two-lever operant box. One-way repeated-measures ANOVA was used to analyze locomotor activity and response rate data. All five compounds stimulated locomotor activity and fully substituted for the discriminative stimulus effects of methamphetamine with similar potencies; however, locomotor stimulation efficacy fluctuated between compounds. 2-FA, 3-FA and 3-FMA produced stimulant effects similar to methamphetamine while 2-FMA and 4-FMA were much weaker stimulants. These results demonstrate the abuse potential of the compounds and indicate locomotor stimulant efficacy does not correlate well with ability to produce methamphetamine-like discriminative stimulus effects; highlighting possible structure-related differences in mechanism that will require further investigation.

Poster 10

Female Rat Ethanol Consumption is not Impacted by Levonorgestrel Administration

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Women are more sensitive to alcohol and at greater risk for alcohol use disorder, with high levels of ovarian hormones (e.g., estrogen and progesterone) associated with increased alcohol intake. In the U.S., about 65% of women use contraceptives, with oral hormonal contraceptives (i.e., The Pill) being most common. However, little is known about their interaction with alcohol. Recent work from our lab suggests that the hormonal contraceptive (HC), Levonorgestrel (LNG) reduces amphetamine preference. LNG is a commonly prescribed progesten-based HC that prevents ovulation and reduces estrogen and progesterone levels. Therefore, we hypothesized LNG would reduce alcohol consumption. The present study examined the effects of voluntary oral LNG (500 µg) administration on alcohol consumption during Pavlovian conditioning in naturally cycling Long-Evans female rats. After undergoing a home-cage drinking procedure to induce alcohol drinking, half of the rats received LNG in vanilla cookie paste, while the other half received just the paste. After alcohol conditioning and extinction training, the rats were tested for long-term extinction memory and reinstatement of alcohol-seeking behavior. Finally, rats were reconditioned and their blood alcohol concentrations (BAC) were assessed. Results showed no significant difference in alcohol consumption or conditioned alcohol-seeking behavior, but LNG rats had significantly lower BACs, suggesting LNG may influence the metabolism of alcohol.

Poster 11

Effects of Social Isolation and Sex on the Propensity to Binge Drink

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Currently, in the United States, binge drinking (BD) accounts for nearly all forms of excessive drinking and cost the U.S. $191 billion in expenses such as criminal justice charges and healthcare expenditures in 2010. While the rates of BD have been decreasing among young adults, BD remains a risk factor for developing alcohol use disorder and females are now reporting higher rates of BD than males. In addition, social isolation is a risk factor for BD. We hypothesized that social isolation would increase ethanol consumption and this propensity to BD in socially isolated rats will be augmented in female rats due to the sex differences in the HPA axis. At postnatal day 21, 28 male and female Long Evans rats were randomly assigned to the pair-housed standard condition (SC) or isolated condition (IC) for 30 days. This study was between subjects, repeated measures and used a modified Intermittent Access to Ethanol (IAE) paradigm to assess BD. After the rearing period, rats had 16 hours of access to ethanol and water 3 times a week for 6 weeks. In addition, a sucrose preference test was administered to 48 male and female Long Evans rats before and after the IAE period. Preliminary sucrose preference results showed that sex, rearing, and ethanol exposure did not influence sucrose preference. Preliminary IAE results suggest that rats, regardless of sex or rearing condition, escalate ethanol drinking over the 6 weeks. We also found a day by sex interaction where female rats escalated their drinking over the 6 weeks while males did not. This suggests that females are quicker to develop alcohol drinking but drink a similar amount as males over the course of 6 weeks. Fur samples will be analyzed to determine the effects of social isolation and ethanol on corticosterone. Future research should examine whether environmental enrichment protects against BD particularly for females.

Poster 12

Morphine tolerance is enhanced by consumption of a high fat/high carbohydrate, but not a ketogenic diet

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Eating a high fat/high carbohydrate diet can lead to obesity; however, other dietary manipulations promote weight loss (i.e., ketogenic diets and food restriction). Patients diagnosed with obesity are prescribed opioids at a higher rate than the general population; however, it is not known if diet impacts morphine-induced antinociception or tolerance. To examine the impact of dietary manipulation on morphine sensitivity, 24 male Sprague-Dawley rats (n=8/diet) were assigned to have free access to a standard (17% kcal from fat), a high fat/low carbohydrate (i.e., ketogenic; 90.5% kcal from fat) diet, or a high fat/high carbohydrate diet (60% kcal from fat). It was hypothesized that rats eating a high fat/high carbohydrate diet would be more sensitive to the antinociceptive effects of morphine as compared to rats eating a standard diet. Morphine-induced antinociception was measured using the warm water tail withdrawal procedure (0.32-56 mg/kg; IP), and rats were injected twice-daily with morphine for 19 days (3.2-56 mg/kg; IP) to induce tolerance. Warm water tail withdrawal latencies were converted to a % maximum possible effect (MPE), averaged by each dietary group, and analyzed using mixed model ANOVAs. There were no group differences in the acute antinociceptive effects of morphine among rats eating different diets. However, the magnitude of tolerance was significantly greater for rats eating a high fat/high carbohydrate as compared to rats eating a ketogenic diet. These results highlight that the acute therapeutic effects of morphine are consistent regardless of dietary intake; however, eating a high fat/high carbohydrate diet can exacerbate tolerance to the antinociceptive effects of morphine. Ongoing data collection to assess the impact of food restriction is also underway to further characterize the impact of dietary manipulation on morphine sensitivity.

Poster 13

Evaluation of 3,4 Methylenedioxypyrovalerone-induced Impulsive Choice in Rats Trained on an Adjusting Delay Discounting Procedure

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Psychostimulant use disorder (PUD) is a public health concern characterized by compulsive substance-seeking behaviors despite adverse risks. Whereas impulsive behaviors are frequently observed in PUD and associated mental health conditions, behavioral assessments of impulsivity are essential to preclinical screening of novel psychoactive substances. Impulsive choice is a quantifiable behavioral measure commonly assessed using delay discounting. The current study replicated and extended a previous study by Hyatt et al. (2019) using a modified experimental design to evaluate the pro-impulsive effects of the synthetic cathinone, 3,4-methylenedioxypyrovalerone (MDPV). Sixteen adult male Sprague-Dawley rats were trained to lever press in a delay discounting procedure with adjusting delays. Training sessions were conducted five days a week and consisted of 15 blocks of trials. Each block of trials included two forced-choice and two free-choice trials. The primary outcome measure, mean adjusted delay (MAD), was calculated across trials. Once rats met stability criteria, a satiety challenge was conducted to determine the effects of feeding on the MAD. Rats were subsequently trained for approximately three weeks until the MAD was stable across five consecutive sessions. Subjects were then divided into two groups, counterbalanced on squad and lever assignment, and matched on the average MAD. These groups were randomly assigned to either the MDPV (N=8) or saline (N=8) treatment group. MDPV (0.1, 0.3, 1.0 mg/kg, I.P.) or saline was administered once per week prior to test sessions. MDPV treatment produced a dose-dependent decline in MAD, but the difference between MDPV and saline-treated rats was not statistically significant at any dose. Although the current study did not evaluate chronic treatment, the preliminary findings with acute MDPV treatment are comparable to previous reports.

Poster 14

Mental health stigma, stress, and cortisol: Implications for substance use disorders

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Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is a risk factor for relapse among those with substance use disorders (SUDs). Importantly, SUDs are often comorbid with other mental health conditions, such as depression, anxiety, and PTSD, which are also associated with dysregulated HPA activity. Stigma around mental illness is likely a common stressor faced by those with comorbid SUD and mental health conditions, but it is unclear to what extent mental health stigma itself could contribute to dysregulated cortisol. This study explored the impact of mental health stigma and support on self-reported stress, mood, and cortisol responses. Participants (n = 39; 80% female, 5% nonbinary) were randomly exposed to either a stigma-inducing or supportive mental health prime and completed surveys that measured stress, mood, and mental health stigma experiences. Although there was no significant difference between the stigma and support primes in cortisol reactivity, stigma significantly increased self-reported stress and negative mood in comparison to the support condition. Participants without a mental health diagnosis reported lower positive mood in response to stigma, whereas those with a diagnosis showed no significant difference, suggesting potential habituation due to regularly being exposed to stigma in the real world. Additionally, participants who perceived higher mental health stigma in everyday life reported higher anxiety and depression. Thus, while the brief stigma prime did not affect cortisol, laboratory and real-world exposures to mental health stigma were associated with higher stress and lower well-being. Interventions to mitigate the impact of mental health stigma could benefit those with comorbid SUD and mental health conditions.

Poster 15

Mouse model of Single Prolonged Stress to induce negative affect and binge-like alcohol consumption

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Exposure to traumatic stressors can have detrimental effects on one's wellbeing. Alcohol is often used as a coping mechanism to alleviate stress, which in some cases can lead to the development of alcohol use disorder (AUD). Despite this interaction, the circuitry recruited during stress and its persistent impact on alcohol consumption and affective behavior is poorly understood. Identifying these circuits will help uncover the mechanisms involved, ultimately leading to better intervention strategies. Here, we highlight the use of a validated preclinical model of PTSD, Single Prolonged Stress, to induce negative affect and binge-like alcohol drinking in mice. Male and female mice underwent a series of stressors of varied modalities after which a full behavior battery and Drinking in the Dark (DID), a validated model of binge-like consumption, were performed. Exposure to SPS differentially alters affective behaviors in males and females, with males being affected more in movement-based behaviors such as novelty suppressed feeding test, and females showing an effect in startle responses. Additionally, prior SPS exposure was sufficient to induce binge-like alcohol consumption, with data suggesting a particularly vulnerable timeframe for intake. Our previous work shows that the insula receives the densest inputs from the basolateral amygdala (BLA) during stress. Ongoing studies aim to chemogentically target the BLA-insula circuit to see how it is involved in these stress-induced affective and drinking behaviors. Overall, our data implicates a potential role of the BLA-insula pathway in regulating the interactions between stress and alcohol related behaviors.

Poster 16

Effects of repeated alprazolam (Xanax) exposure during adolescence on mood-related behaviors and stress susceptibility

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Reports show that alprazolam (Xanax; ALP) is the most abused benzodiazepine (BZD) among adolescents. In adults, repeated exposure to BDZs can lead to adverse effects including a rebound of anxiety during periods of abstinence. Given that adolescence is a sensitive period of development marked by heightened sensitivity to stress and drugs use/abuse, this study was designed to investigate the effects of repeated ALP exposure on stress susceptibility and responsivity to environments inducing anxiety- and depression-like behaviors. Adolescent male mice (postnatal day [PD] 35) were exposed to vehicle (VEH) or ALP (0.5 mg/kg) once daily from PD 35-49, and were then tested on various behavioral assays (i.e., open field test [OFT], three-chamber sociability test, elevated-plus maze [EPM], and the forced swim test [FST]) 24-h (short-term; ST) or 1-month (long-term; LT) after drug cessation. In a separate cohort, mice received ALP as described and then subjected to chronic social defeat stress (CSDS) after drug cessation to assess their sensitivity to stressful circumstances. In the ST groups, we observed significant increases in time spent in the center of the OFT and social interaction and decreases in immobility in the FST (no stress susceptibility) when compared to VEH-treated controls. In the LT groups, we observed significant increases in social interaction and increases in time spent immobile in the FST (stress susceptibility) when compared to VEH-treated controls. Our results indicate that repeated ALP treatment during adolescence dysregulates mood-related behaviors in the LT that can profoundly influence susceptibility to stressful circumstances in adulthood.

Poster 17

Analyzing the relationship between behavioral and physiological responses to chronic ethanol intake in dependent and non-dependent mice using multidimensional profiling

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Ethanol (EtOH) dependence has been shown to change the excitability of dopamine D1 receptor-expressing medium spiny neurons (D1MSNs) in the nucleus accumbens (NAc) of male mice. Here, we investigated possible behavioral and physiological differences in both sexes using an established model of EtOH dependence and multi-dimensional profiling. Briefly, mice underwent a two-bottle choice (2BC) paradigm (15% EtOH versus water, 2 h/day). Following 21 days baseline 2BC, EtOH dependence was induced over 4 bouts of chronic intermittent ethanol vapor exposure (16 h/day for 4 days followed by 3 days of no vapor and 5 days of 2BC). Non-dependent and ethanol naïve handling controls received air vapor. Brains were removed 24 h after the final vapor exposure and slices containing the NAc were made. D1MSN excitability and membrane properties were measured using whole-cell patch clamp electrophysiology. Data from individual neurons was standardized into z scores, according to sex, and electrophysiological profiles were created from 16 electrophysiological measures using principal component analysis (PCA) and k-means clustering. PCA reduced dimensionality and determined the appropriate number of components, while k-means clustering identified individuals from PCA and designated two cluster profiles. Contrary to our expectations, assignment to Cluster 1 (30 neurons:15F,15M; 12 naïve, 10 non-dependent, 8 dependent) and Cluster 2 (50 neurons:29F,21M; 20 naïve, 15 non-dependent, 15 dependent) did not align with treatment condition or sex (no significant differences in distributions of treatment condition, X2 (2, n=36)=0.14, p=0.93, or sex, X2 (1, n=36)=0.48, p=0.49, between Clusters 1 and 2). This indicates the identification of latent profiles in electrophysiological data, and further investigation of these cluster profiles is needed to clarify the relationships between NAc D1MSN physiology and behavior following chronic ethanol experience.

Poster 18

Investigating the impacts of organic cation transporter 3 depletion on astrocyte morphology and expression: Potential impacts for amphetamine-type use disorder

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In the ventral tegmental area (VTA) of the mesolimbic reward circuit, a recent report suggests that astrocytes actively elevate calcium signalling and control motor behavior in response to amphetamine administration (PMID: 31954621). Thus, a more complex interplay between astrocytes and dopamine (DA) neurons in reward centers is likely at play, raising the possibility that astrocytes have an important role in stimulant use disorders (SUD). Given our findings that organic cation transporter 3 (OCT3), which is richly expressed on astrocytes, as well as neurons, is an important player in the neurochemical and behavioural effects of amphetamine (PMID: 38072333), we sought to gain preliminary insights into how loss of OCT3 impacts astrocyte expression and morphology. OCT3 is a low-affinity high-capacity DA transporter. We have shown that a substantial component of amphetamine-evoked DA release is OCT3 dependent and mice with global knockout of OCT3 fail to develop conditioned place preference for amphetamine (PMID: 34948221) or to self-administer amphetamine (unpublished). Here, we hypothesize that OCT3 is a key regulator of astrocyte expression and morphology, which might in turn contribute to the magnitude of neurochemical and behavioral effects of amphetamine. Using OCT3 wildtype and knockout mice, we performed immunohistochemical characterization of astrocytes in VTA and hippocampus. Our preliminary results indicate increased gliosis in both brain regions of OCT3 knockout mice, characterised by greater fluorescent intensity of the pan-astrocyte marker (GFAP), increased number of astrocytes, along with increased complexity of astrocyte processes. Although preliminary, our results have potential ramifications for the impact of how gliosis in reward centers of brain may be protective or pathological in SUD. Our ongoing studies are investigating astrocyte OCT3 as a novel target for development of treatments for amphetamine-type SUDs.

Poster 19

The effects of repeated alprazolam exposure during adolescence on the dysregulation of drug-reward sensitivity and mood-related behaviors

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Alprazolam (Xanax; ALP) is a potent, short-acting benzodiazepine (BDZ) commonly prescribed to treat anxiety disorders. However, despite displaying concerning trends in affiliation with the opioid epidemic, along with sex-differences in both medical and nonmedical use in adolescent populations, clinical data has yet to fully present the effects of ALP in females. This study therefore aimed to investigate the influence of repeated ALP exposure during adolescence on drug-reward and stress response in female mice. Female adolescent C57BL6/J mice were pretreated with vehicle (VEH) or ALP for 14 days. 24-h following the last injection, a sample of mice were exposed to conditioned place preference (CPP) with nonrewarding doses of morphine to examine sensitivity to drug reward. In order to characterize ALP-induced reactivity to stress, a separate cohort of mice were exposed to the open field test (OFT), the elevated plus maze (EPM), the Crawley's three-chamber sociability test, and the forced swim test (FST). ALP-pretreated groups, compared to VEH-pretreated groups, showed indication for dysregulation of drug reward sensitivity where a low dose of MOR induced avoidance-like behavior. In addition, our results indicate that ALP exposure influences behavioral responses to stress in a complex manner where exploratory behavior is increased while sociability and latency to immobility significantly decreased. Our findings have important clinical implications as BDZs such as ALP are both prescribed/used more frequently among women than men resulting in an increased risk for developing substance use disorder(s) and experiencing increased sensitivity to stress.

Poster 20

Cocaine Modulates Clearance of Dopamine in the Basolateral Amygdala in a Dopamine Concentration-Dependent Manner

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Cocaine use disorder (CUD) is complex and often comorbid with stress-related disorders. Cocaine inhibits the dopamine (DA) transporter (DAT), a high-affinity, low-capacity (uptake 1) transporter that removes DA from the extracellular milieu. Volume transmission of DA is a vital component of the reward-related properties of cocaine. Stress can also prolong DA clearance via blockade of the corticosterone-sensitive organic transporter cation 3 (OCT3), a low-affinity, but high-capacity (uptake 2) transporter for DA. The basolateral amygdala (BLA) is an important brain structure in reward circuitry and stress reactivity, which contains both DAT and OCT3. We hypothesized that in BLA, the ability of cocaine to inhibit DA clearance is reduced under conditions of high ambient levels of extracellular DA. To test the capacity of cocaine to inhibit DA clearance in a concentration dependent fashion, we used in vivo highspeed chronoamperometry in C57BL/6 mice. We found that at "low" DA concentrations (~0.5 µM), cocaine (n= 7 mice) robustly increased DA signal amplitude and prolonged the time for DA to be cleared by 80% of peak amplitude (T80) compared to vehicle (n=9), consistent with cocaine's well-known mechanism of action to block uptake 1 transporters. In contrast, at "high" DA concentrations (~2.0 µM), cocaine (n=4) had no impact on signal amplitude but still prolonged T80 compared to controls (vehicle, n=5), consistent with uptake 1 transporters dominating as extracellular DA levels fall to lower micromolar ranges. These results support a growing body of evidence showing an important role of uptake 2 transporters, putatively OCT3, in determining the magnitude of the effect of uptake 1 blockers, like cocaine. Future studies investigating concomitant blockade of uptake 1 and 2 transporters in BLA and the role of OCT3 in monoamine clearance in BLA in stress-related pathologies and CUD are warranted.

Poster 21

Oxytocin rescues cocaine-induced euphoria as measured through female rat ultrasonic vocalizations

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Cocaine craving and euphoria are well-documented reinforcers of cocaine addiction, though current behavioral models do not fully address these affective states. Ultrasonic vocalizations (USVs) are high-frequency noises produced by rodents throughout their lifespan to signal affective states. These calls can be classified into positive-state high-frequency (50 kHz) calls and negative-state low-frequency (22 kHz) calls. USVs allow for the measurement of cocaine effects and provide insight into potential therapeutic targets. Oxytocin (OXT) is a potential pharmacotherapeutic capable of attenuating cocaine addiction behaviors, however, the effect of OXT on cocaine-induced affective responding has not been fully investigated. We hypothesized that administration of OXT would have a protective effect on the positive affective state induced by cocaine, as measured through changes in positive-state high-frequency USVs. To assess this, we used female Long-Evans rats (n = 30) divided into 3 groups: saline-saline, saline-cocaine, or cocaine-OXT, then assessed USVs across 3 days. On day 1, we measured baseline USVs for 20 minutes without treatment. On days 2 and 3, each group was injected with cocaine (20 mg/kg; i.p.) then USVs were assessed 20 minutes later. Using univariate ANOVAs, we found that cocaine administration significantly increased positive-state high frequency calls for saline/cocaine animals relative to controls across both treatment days. Importantly co-administration of OXT (3 mg/kg; i.p.) rescued the observed cocaine-induced increase in positive-state high frequency calls. These results suggest that OXT may effectively offset cocaine-induced changes in affective state, highlighting OXT's pharmacotherapeutic utility and underscoring USVs as a tool to measure these changes.

Poster 22

Influence of Prior Differential Reinforcement of Low Rate Behavior Training on Amphetamine-Induced Impulsivity and Inhibitory Control in Rats

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Substance use disorders (SUD) present a complex interaction of neurobiological, psychological, and social factors affecting millions of individuals globally. Understanding the role of behavior inhibition in SUDs is critical to their prevention and treatment. Behavior inhibition can be assessed experimentally in rodents by utilizing an operant conditioning schedule known as differential reinforcement of low rate responding (DRL). Previous studies utilizing DRL schedules have shown psychostimulant drugs reduce behavior inhibition, as indicated by more rapid responding and consequential reinforcement loss. To our knowledge, the influence of differential training history on drug-induced disruption of impulse control has not been evaluated. This study utilized DRL 18 s and 72 s schedules to assess the influence of prior learning history on amphetamine-induced impulsive action. Sixteen adult male Sprague-Dawley rats were trained to lever press for food reinforcement under either a DRL 18 s (N=8) or DRL 72 s (N=8) schedule until responding was stable. Both training groups were subsequently tested following d-amphetamine (0.5, 2.0 mg/kg) or saline injections under both DRL 18 and DRL 72 schedules in series of weekly test sessions. Results indicate statistically significant differences between training groups in the number of responses and reinforcers earned, with the DRL 72 s trained rats showing decreased behavioral inhibition following amphetamine treatment. These findings suggest the importance of considering prior training history to understand drug-induced impulsivity. Future research directions include the replication of this study in female rats to evaluate potential sex differences in behavior inhibition.

Poster 23

Reversal learning performance in male and female mice following an acute stressor

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Reversal learning is used to evaluate cognitive flexibility. Inflexibility has been implicated in substance use disorders and relapse. Chronic stress can compound inflexibility symptoms, but the effects of acute stress are less clear, particularly in females. We hypothesized that in the absence of stress, male mice would adjust faster to a rule reversal than females, that acute stress exposure would lengthen reversal adjustment time in both sexes, and that these stress effects would be augmented in females. Male and female mice were exposed to an acute stressor, then underwent one or two rule reversal(s) in an appetitive operant lever-pressing task. All mice underwent a rule reversal 7 days after acute stress (distal from stressor); the group experiencing two rule reversals also had a reversal proximal to (24 h later) the stress. Data collection is ongoing (N=5-8 per group). Groups were analyzed within reversal number, each with two-way repeated measures ANOVAs (sex × stress × time) and pairwise comparisons with Bonferroni correction. Aside from an expected main effect of time ($p<0.001$), there were no interactions nor main effects in the one reversal group (all $p>0.20$). In the two reversal group, there was again an expected main effect of time ($p<0.001$) as well as a significant sex × stress interaction ($F(1,16)=5.39$, $p=0.034$, partial $\eta 2=0.25$). Pairwise comparisons indicated stress temporally proximal to a rule reversal improved female, but not male, performance, and that prior rule reversal experience quickened male, but not female, adjustment in the absence of stress. Future manipulations will uncover molecular mechanisms that underpin sex-selective responses following stress. Understanding molecular functions will enable development of neuropharmacological treatments to facilitate cognitive flexibility in individuals struggling with substance use disorders and minimize instances of relapse.

Poster 24

Enhanced response to nicotine in stress-induced reinstatement and increases in accumbal CREB in a heritable rodent model of schizophrenia

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Schizophrenia (SZ) is characterized by hallucinations, delusions, anhedonia, and cognitive deficits, alongside a high smoking comorbidity—3 to 4 times greater than the general population. Smoking in SZ worsens antipsychotic efficacy, life expectancy, and quality of life, with stress further exacerbating relapse risks. Smoking cessation is particularly challenging, as it often intensifies SZ symptoms. Our laboratory has established a heritable rodent model of psychosis and drug abuse vulnerability. In this model, Sprague-Dawley rats are neonatally treated with saline (NS) or quinpirole (NQ), a dopamine (DA) D2-like agonist (1 mg/kg), from postnatal days (P)1-21. NQ-treated rats display a lifelong supersensitization of the DAD2 receptor, a hallmark of psychosis. In the present study, F1 generation offspring of two NS (MSxFS) or two NQ-treated (MQxFQ) rats underwent nicotine conditioned place preference (CPP), extinction and stress-induced reinstatement. On P41-42, MSxFS and MQxFQ rats were given a saline pre-test, and then conditioned to nicotine (0.6 mg/kg base) from P43-50. On P51, animals were given a drug free post-test. MQxFQ rats demonstrated enhanced expression of nicotine CPP. On P52-P59, animals underwent extinction testing, with MQxFQ rats demonstrating significant resistance to extinction. On P60, animals were exposed to restraint stress 30 min prior to the reinstatement trial. The MQxFQ group demonstrated robust reinstatement, whereas F1 MSxFS animals did not show reinstatement. Brain tissue was taken 1 h after restraint stress and analyzed for CREB within the nucleus accumbens. CREB was significantly increased in MQxFQ rats administered saline, with nicotine possibly having a neuroprotective effect. The present study is the first to investigate nicotine stress-induced reinstatement in a heritable rodent model of psychosis and drug abuse vulnerability.

Poster 25

Alprazolam withdrawal increases home cage locomotor activity and induces an insomnia-like phenotype in adult male and female mice

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A stark increase in benzodiazepines (BZDs) use and abuse has led to alarming rates of overdoses, with alprazolam (Xanax®; ALP) as the most abused BZD worldwide. Despite these alarming trends, understanding of the neural mechanisms driving BZD withdrawal remains critically limited. BZDs are among the most dangerous drugs to withdraw from, and no established behavioral measures exist to assess the neurobiology underlying their withdrawal symptomatology. Therefore, this study seeks to establish standard behavioral measures of ALP withdrawal in mice, in order to further investigate the circuitry and molecular mechanisms underlying BZD withdrawal and uncover potential novel treatments. We hypothesized that ALP-treated mice will exhibit behavioral and physiological symptoms resembling the human condition in a spontaneous withdrawal context. Adult male and female mice received ALP (0.1 mg/ml) or vehicle (VEH) ad libitum for 16 days (n = 12–16/group). On days 15 and 16, mice home cage behaviors (i.e., locomotor activity, sheltering, and sleeping) were tracked using automated behavioral monitoring units. On day 17, ALP was removed and replaced with a two-bottle choice (water or 0.8% sucrose) to assess withdrawal effects. During drug exposure, ALP-treated mice showed increased sheltering, reduced locomotor activity, and increased sleep compared to VEH-treated controls. In contrast, ALP-treated mice exhibited higher locomotor activity and reduced sleep than VEH-treated controls during withdrawal. In summary, ALP reduces locomotor activity and increases sleep, while its withdrawal increases locomotor activity and induces an insomnia-like phenotype.

Poster 26

Nictotinic Modification of Cocaine's Reinforcing Effects in Squirrel Monkeys

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Preclinical and clinical studies suggest that nicotine may enhance the reinforcing effects of cocaine. The present study in male squirrel monkeys (N=4) responding under concurrent FR schedules of intravenous (IV) injections or food delivery ('choice') was conducted to determine whether other nicotinic agonists developed as medications for smoking cessation, i.e., the partial agonists varenicline (Chantix®) and cytisine (Tabex®) may similarly modify cocaine's reinforcing effects. Results show that IV cocaine was robustly self-administered under choice conditions: the number of injections per session was low and responding occurred predominantly on the food-associated lever when IV saline was available whereas the number of injections per session increased dose-dependently, with concomitant decreases in the number of food deliveries, when IV cocaine was available. Pretreatment with both nicotine (0.01 – 0.1 mg/kg) and cytisine (0.01 – 0.1 mg/kg) produced dose-dependent leftward shifts in the cocaine dose-response curves for 'choice' (% responding on the injection-lever) and increased intake (injections per session) of unit doses of cocaine on the ascending portion of the bitonic dose-response curve. Maximal increases in the ED50 for cocaine choice were produced by 0.18 mg/kg nicotine (~3-fold) and 0.32 mg/kg cytisine (~12-fold). Of interest, the nicotinic partial agonist varenicline, up to a dose that markedly decreased rates of responding (0.1 mg/kg), did not consistently modify cocaine's reinforcing effects in a similar manner. Averaged data indicate that pretreatment with the highest dose of varenicline elevated the number of self-administered injections of lower unit doses of cocaine (0.003 and 0.01 mg/kg) and flattened the bitonic dose response curve for cocaine intake. These results are consistent with previous findings regarding nicotine's modulation of cocaine self-administration and suggest that nicotinic partial agonists including cytisine and, to a lesser extent, varenicline, also may enhance cocaine's abuse-related reinforcing effects.

Poster 27

Quantification of observable behaviors induced by mu- and kappa-opioid agonists in Rhesus monkeys

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Kappa-opioid receptor agonists (KORAs) have been evaluated as potential therapeutics for pain, pruritus, and substance-use disorders. Typical KORAs show side-effects like dysphoria and sedation. Atypical KORAs that are putatively G-protein biased have been reported to produce therapeutic-like effects with reduced side effects compared with typical KORAs. This study investigated HS665, an atypical, putatively G-protein biased, KORA and compared it with 2 other KORAs (i.e., U50-488h, a prototypical KORA, and triazole 1.1, a putatively G-protein biased KORA of a different structural class than HS665). Adult female (n=2) and male (n=2) rhesus monkeys were intravenously administered oxycodone (a mu-opioid agonist; 0.010.56 mg/kg), U50-488h (0.01-0.1 mg/kg), triazole 1.1 (0.1-1.0 mg/kg), and HS665 (0.01-0.32 mg/kg). Species-typical and drug-induced behaviors were scored by blinded observers. Oxycodone induced dose-dependent increases in scratching and facial rubbing, a putative indicator of gastrointestinal distress. When given alone, the KORAs did not induce scratching or facial rubbing. U50-488h and HS665 caused dose-dependent reductions in species-typical behavior. All KORAs reduced scratching in a dose-dependent manner. However, HS665 more resembled U50-488h, where doses that reduced scratching also reduced species-typical behaviors whereas doses of triazole 1.1 that reduced scratching did not affect species-typical behaviors. These results suggest that putatively G-protein biased KORAs do not always offer more favorable side-effect profiles. The study further indicates that triazole 1.1 may have unique mechanisms for selectively reducing pruritus without causing other side effects.

Poster 28

Impulsivity and brain metabolite alterations in recently abstinent methamphetamine users

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Background: Methamphetamine is a highly addictive psychostimulant that induces neurocognitive deficits, neurochemical changes, and increased impulsivity, contributing to high relapse rates. However, the relationship between impulsivity and neurochemical alterations in recently abstinent methamphetamine users (MA) remains unclear. This study examines alterations in key brain metabolites—myo-inositol (INS), N-acetylaspartate (NAA), glycerophosphocholine+phosphocholine (GPC+PCh), and glutamate+glutamine (Glu+Gln)— in fronto-striatal regions and their relationship with impulsivity. Methods: 14 MA and 15 age-matched controls (aMC) underwent magnetic resonance spectroscopy (MRS) scans (3.0T Siemens MRI). Single voxel spectra were acquired from the dorsolateral prefrontal cortex, medial prefrontal cortex, caudate, and anterior cingulate cortex. Metabolite levels were quantified as ratios to phosphocreatine+creatine (PCr+Cr). Impulsivity was assessed using the Barratt Impulsiveness Scale (BIS-11), and correlations between metabolite levels and impulsivity were analyzed. Results: MA group exhibited increased NAA/PCr+Cr in the caudate and decreased Glu+Gln/PCr+Cr in the anterior cingulate and caudate compared to aMC group. They also had higher motor impulsivity scores. In aMC, caudate NAA/PCr+Cr correlated significantly with motor impulsivity (r = .73, p = .003), a relationship absent in MA group. Conclusions: Methamphetamine use may induce neuroinflammation, neurotransmitter dysfunction, and neuronal damage in striatal regions. The relationship between motor impulsivity and methamphetamine-induced neurotoxicity may underlie relapse vulnerability. These findings highlight the potential of brain metabolites as biomarkers for methamphetamine-related brain damage.

Poster 29

Decoding behavioral economics vs. traditional dose response functions in intravenous animal drug self-administration procedures

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Behavioral economics (BE) and demand curve analyses of drug consumption have gained in popularity as a novel analytical strategy for the assessment of addiction-related phenotypes using animal models. These analyses determine how the consumption of drug reinforcers change as a function of cost. In contrast, older dose response curve (DRC) analyses summarize this relationship by illustrating the number of infusions obtained at each dose. Despite the analytical differences between BE and DRC analyses, the nature of the data employed is identical across these strategies. However, the limited understanding of the similarities, differences, advantages and disadvantages of each approach hinders comparisons across studies. Data from rats self-administering fentanyl in a within-session dose response program were used to generate parallel shifts, changes in the ascending and descending limbs, among other simulations to determine subsequent differences in demand intensity (Q0) and elasticity (α) using BE analyses. Combining insights from both fields will enhance comprehension and unite these analytical approaches to identify therapeutics and improve translational outcomes related to substance use disorders.

Poster 30

2,5-Dimethoxy-4-Iodoamphetamine Sex-Dependently Augments Head Twitch Response in Rats Chronically Treated with Oxycodone

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Opioid use disorder (OUD) is a public health emergency with serious physical and social consequences including disability, relapse, and death (CDC). In 2023, opioid-related overdose deaths exceeded 80,000. OUD is characterized by rapid escalation of intake due to tolerance and downregulation of the mu-opioid receptor which drives negative reinforcement and withdrawal. Mu-opioid receptor alterations are a major contributor of continued use. Evidence indicates that that the serotonin (5-HT) 5-HT2A receptor (5-HT2AR) regulates the desensitization and downregulation of the mu-opioid receptor, although the interaction between the 5-HT2AR and mu-opioid receptors is not well characterized. This study examined the effects of chronic mu-opioid receptor activation on the head-twitch response (HTR), a behavioral proxy for 5-HT2AR-mediated hallucinogenic activity. We hypothesized that chronic oxycodone exposure downregulates mu-opioid receptors and augments DOI induced HTRs, and that female rats treated with oxycodone would show the greatest HTR increase. Analysis indicated that DOI dose-dependently increased HTR in saline and oxycodone-tolerant rats. Biological sex enhanced the potency of DOI in female but not males in oxycodone-tolerant rats. Follow-up time-course analysis determined that across the 30minute assay, females had elevated HTRs throughout each analyzed time bin while males increased HTRs was more variable, suggesting that the onset of DOI is altered by sex and oxycodone exposure. These results provide strong evidence that the mu-opioid receptor and 5-HT2AR have a functional interaction revealed by a behavioral assay.

Poster 31

Immunomodulatory effect of α-terpineol on precipitated nicotine withdrawal behavior in mice

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Nicotine withdrawal impacts the immune system of tobacco smokers trying to quit. The immune changes involved have not been fully characterized, especially in the ventral striatum, the cerebellum, and plasma. Cannabinoid type 1 receptor (CB1R) and type 2 receptor (CB2R) agonists are potential treatments to manage nicotine withdrawal symptoms. The terpene, αterpineol, is found in cannabis and acts as a mixed CB1R and CB2R agonist with potential anti-inflammatory effects. We hypothesized that α-terpineol could alter withdrawal-related behaviors in a mouse model of nicotine withdrawal, as well as impact corresponding immune responses. Sixty-three male and female C57/BL6J mice were treated daily with four 2 mg/kg nicotine or saline subcutaneous injections. On day 14, mice received a single intraperitoneal (i.p.) injection of treatments, then, either 56 mg/kg α-terpineol or its vehicle. Mecamylamine (3mg/kg i.p.) was administered to all mice to precipitate nicotine withdrawal. Behavioral signs of withdrawal were recorded. Brain regions and plasma were collected for Luminex assay to quantify the mean concentrations of monocyte chemotactic protein-3 (MCP-3), interferon gamma-inducing protein-10 (IP-10), and thymic stromal lymphopoietin (TSLP) proteins. One-way and two-way ANOVA with appropriate post-hoc tests were used for analysis. Nicotine + vehicle female mice had the highest total withdrawal signs which α-terpineol abolished. Nicotine + vehicle male mice had an increased mean cerebellar concentration of TSLP. This indicates withdrawal may enhance inflammatory signaling in discrete brain regions. Plasma MCP-3 was elevated in female nicotine + vehicle mice but decreased in female nicotine + αterpineol mice. IP-10 was significantly reduced in the plasma from nicotine + vehicle and nicotine + α-terpineol mice. Together, these data suggest that α-terpineol attenuates nicotine withdrawal and produces anti-inflammatory effects in a sex-dependent manner.

Poster 32

Environmental enrichment attenuates reinstatement of heroin seeking and reverses heroin-induced upregulation of mesolimbic ghrelin receptors

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Opioid use disorder is a widespread and detrimental health crisis. Current treatments are opioid-based and pose risks of dependence and respiratory failure. As a result, there emerges a fundamental need to search for novel therapeutic approaches and to identify underlying mechanisms that contribute to relapse. This study aimed to assess if environmental enrichment (EE)--a method of stimulating physical, social, and cognitive engagement–could attenuate heroin-seeking behavior in animals with a history of extended access to heroin self-administration. Mechanistically, we sought to investigate whether heroin self-administration causes neuroadaptations of ghrelin receptors (GHS-R1a) and whether EE could reverse these effects. During extinction and cue-induced reinstatement test, EE rats showed a significant reduction in active lever responding compared to non-EE rats, suggesting that EE facilitates extinction of drug seeking and reduces the capacity of drug-associated stimuli to elicit and maintain drug seeking. Using Western Blotting, we found that rats with LA to heroin IVSA showed a significant increase in ghrelin receptor (GHS-R1a) expression in the ventral tegmental area and nucleus accumbens, the brain regions implicated in relapse. Exposure to EE attenuated heroin-induced upregulation of GHS-R1a receptor in these regions but produced no significant changes other brain regions. Our findings suggest that EE can attenuate heroin seeking and related neuroadaptations of GHSR1a receptors. As such, EE is a non-opioid-based therapeutic approach that possibly might effectively mitigate addictive behaviors and combat the opioid crisis.

Poster 33

Buprenorphine attenuates the reinforcing effects of fentanyl in rhesus monkeys

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Buprenorphine is the most widely prescribed medication for opioid use disorder and can attenuate the effects of opioid agonists (e.g., heroin). However, the illicit opioid supply has become saturated with the highly potent mu-opioid receptor agonist fentanyl, and the effects of buprenorphine on the reinforcing effects of fentanyl are not well characterized. The present study examined the effects of buprenorphine on fentanyl that was intravenously self-administered by rhesus monkeys (3 males, 1 female) twice daily (maximum 30 infusions/session). First, fentanyl dose-effect curves (0.032-1.0 ug/kg/infusion) were determined and a unit dose resulting in a high number of infusions was identified and available in subsequent sessions. Buprenorphine (0.032- 1.0 mg/kg) was administered intravenously 30 minutes before a morning session, and the effects on fentanyl self-administration were studied for at least 3 days. Buprenorphine dose-dependently decreased fentanyl self-administration, but the onset of action and potency of buprenorphine varied among monkeys. In two monkeys, 1.0 mg/kg buprenorphine decreased responding the day of administration, whereas the effects of buprenorphine were not observed until the day after administration in the other monkeys. In one monkey, 0.1 mg/kg buprenorphine decreased fentanyl self-administration modestly, but larger doses were needed to decrease responding in the other three monkeys. To determine if the delayed onset of action of buprenorphine observed in some monkeys could be due to shared subjective effects between buprenorphine and fentanyl, saline was substituted for fentanyl and 0.32 mg/kg buprenorphine was administered before a morning session. Here, all monkeys obtained a high number of saline infusions the day of administration before responding for saline extinguished across subsequent sessions. These data demonstrate that buprenorphine can dose-dependently attenuate the reinforcing effects of the highly potent mu-opioid receptor agonist fentanyl, and that the delayed onset of action of buprenorphine observed herein could be due to shared subjective effects between drugs.

Poster 34

Alprazolam (Xanax) exposure during adolescence exacerbates spontaneous morphine withdrawal and dysregulates second messenger signaling within the VTA-NAc pathway

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Reports show that patients seeking treatment for opioid use disorder and/or withdrawal are commonly benzodiazepine (BZD) co-dependent as well. Concomitant ingestion of alprazolam (Xanax; ALP) and opioids is common, and it has also been reported in the adolescent population, increasing the risk for developing substance use disorders (SUDs) and overdose death. Therefore, this study was designed to investigate the neurobiological effects of ALP exposure during adolescence on spontaneous morphine (MOR) withdrawal. Adolescent male mice (postnatal day [PD] 35) received vehicle (VEH) or ALP (0.5 mg/kg) once daily (PD35-49). On PD50, they received twice daily VEH or escalating doses of MOR alone, or in combination with ALP for 6 days, to induce tolerance and physical dependence. On day 7, the mice received a challenge dose of MOR (20 mg/kg), and spontaneous withdrawal signs were assessed 2, 4, 8, and 24 h after the MOR challenge. Mice pretreated with ALP exhibited significant weight loss during MOR exposure and the 24 h after MOR discontinuation. ALP-pretreated mice also exhibited significant increases in total withdrawal signs (i.e., jumping, chewing/licking, paw tremors, headshakes) when compared to the VEH-MOR-treated controls. In addition, ALP pretreatment induced decreases in TH, ERK2, Akt, and mTOR signaling in the VTA-NAc reward pathway. These findings indicate that ALP exacerbates opioid withdrawal symptoms, dysregulating second messenger signaling in reward-related brain pathways. Together, these findings have critical implications for the perpetuation of SUDs as potentiated withdrawal symptoms can drive the continuation of drug use.

Poster 35

Evaluation of serotonin 2C and dopamine D3 receptor ligands as candidate medication to reduce self-administration of opioids and stimulants in rats

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Rates of substance use disorder (SUD) are at an all-time high. Despite this, there are few FDA approved drugs to treat SUDs and none approved for stimulant use disorders. Preclinical studies have found that agonists at the serotonin 2C receptors (5-HT2CR) as well as antagonists and partial agonists at the dopamine D3 receptors (DAD3Rs) reduce self-administration across multiple classes of drugs. However, these drugs have off-target effects that limit clinical utility. The current studies evaluated the potency and effectiveness of a combination therapy targeting 5-HT2CRs (CP-809101; 0.18-5.31 mg/kg) and DAD3Rs (VK4- 40 and VK4-116; 1.88-43.66mg/kg) to reduce the self-administration of fentanyl (0.0032 mg/kg/inf), cocaine (0.32 µg/kg/inf), methamphetamine (0.056 mg/kg/inf) and sucrose (1 pellet) in male and female Sprague-Dawley rats (n=8-10/group). Rats were allowed to respond under a progressive ratio schedule of reinforcement with pretreatments of CP-809101 with either VK4-40 or VK4-116 administered via IP injection, 15 min prior to the start of the session. All treatments tested alone dose-dependently decreased drug-taking, with CP-809101 being the most potent and effective. Combining CP-809101 with either VK4-116 or VK4-40 resulted in a dose dependent and complete inhibition of responding for cocaine, methamphetamine, and fentanyl. Importantly, mixtures were less potent and effective at decreasing responding for sucrose. These data suggest that a combination of highly selective 5-HT2CR agonists, and either partial agonists or antagonists of the DAD3R might have broad spectrum effectiveness as novel treatments for (poly)substance use disorders.

Poster 36

Identifying the differential expression profile of astrocyte-expressed genes during alcohol withdrawal

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Alcohol use disorder affects 29 million Americans annually1, 3, 6, 7. Studies suggest that astrocytic proteins in the amygdala drive negative emotional withdrawal symptoms4, 5. Dependence-associated changes in astrocytic gene expression in the central nucleus of the amygdala (CeA) and basolateral amygdala (BLA) are poorly understood. We hypothesize that chronic intermittent ethanol vapor exposure (CIE) elicits differential expression profiles in astrocyte-expressed genes across withdrawal stages in amygdala nuclei. Adult male Wistar rats (n=46) underwent CIE [5 weeks; blood alcohol levels: 175-225 mg%]. Rats were sacrificed during acute (8-10 hours) or protracted withdrawal (6 weeks)2. To identify withdrawal-related astrocyte candidates (*Gfap, Lcat, Tnc, Ankrd29, Map3k19, Wdr49, and Veph1)*, I performed qPCR. In the CeA, *Wdr49* increased 11-fold increased after protracted withdrawal ($p<0.0001$). In the BLA, *Wdr49* increased 7-fold in acute withdrawal ($p<0.0001$); *Tnc*, *Map3k19,* and *Wdr49* increased 5, 7, and 9-fold respectively in protracted withdrawal ($p<0.05$). Principal component analysis showed regional changes in marker covariances across withdrawal stages; CeA *Ankrd29* was uncorrelated with other CeA markers in controls, positively correlated in acute withdrawal, and inversely correlated in protracted withdrawal. In acute withdrawal, k-means clustering discriminated CIE subjects with increased BLA *Wdr49, Lcat,* and *Tnc*. BLA *Wdr49*, *Tnc*, and *Lcat* became intercorrelated, unlike in controls; CeA *Map3k19* became associated with CeA *Tnc*. In protracted withdrawal, k-means clustering discriminated CIE subjects with increased CeA *Wdr49* and BLA *Wdr49*, *Map3k19*, and *Ankrd29* expression. BLA *Map3k19* and *Ankrd29* became associated with BLA *Gfap*, *Tnc*, and *Wdr49*; conversely, BLA *Map3k19- Veph1* association decreased. CeA *Wdr49* correlates with BLA *Map3k19*, *Wdr49* and *Gfap*. CeA and BLA *Gfap* were no longer correlated, unlike in other groups. We will examine the functional roles of amygdala nucleus - and withdrawal stage – specific changes in (co)- expression profiles of astrocytic genes.

Poster 37

Behavioral microstructure of alcohol seeking in mice

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Preclinical animal models are essential for developing effective strategies to prevent and treat alcohol use disorder (AUD). A key aspect of this research is accurately assessing alcohol's reinforcing efficacy—its ability to drive and sustain seeking behaviors—and its sensitivity to interventions. Existing methods often lack specificity and theoretical grounding. This multiphase study examined whether alcohol-seeking behavior in mice is organized into bouts and whether parameters of this organization—bout initiation rate, within-bout response rate, and mean bout length—serve as indicators of motivational states and alcohol's reinforcing efficacy. Mice were assigned to one of two reinforcers: a 20% ethanol/20% sweetened condensed milk solution (EtOH) or a 20% sweetened condensed milk solution (SCM) in water. In Phase 1, mice were reinforced on a variable time (VT) 60-s fixed ratio (FR) 5 schedule and allowed 1–4 or 5 reinforcers per trial depending on condition. Phase 2 followed the same structure but limited mice to one reinforcer per trial. Bayesian hierarchical analysis of inter-response times (IRTs) confirmed that alcohol-seeking behavior is organized in bouts, with EtOH mice exhibiting lower bout-initiation and within-bout response rates. Additionally, reducing reinforcer magnitude increased bout-initiation rates and shortened post-reinforcement pauses (PRPs) in both conditions. These findings establish a theoretically grounded framework for assessing alcohol's reinforcing properties in preclinical models.

Poster 38

Self-administration of benzodiazepines in drug-naïve and cocaine-experienced rhesus monkeys: role of alpha subunit-containing GABAA receptors

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Benzodiazepines (BZs) are safe and effective therapeutics, however, BZs have unwanted side effects like their potential for misuse. BZs bind at the interface of the α and γ subunit on the GABAA receptor, with the α1, α2, and α3 subunit-containing receptors likely involved with their reinforcing effects. Compounds that lack efficacy at the α1 subunit (α1-sparing compounds) appear to have reduced potential for misuse, though their reinforcing effects are dependent upon past drug experience. Choice procedures were used to evaluate whether drug-naive and cocaine-experienced subjects self-administered α1-sparing compounds when substituted for food or cocaine, respectively. Female (n=2/drug experience group) and male (n=2/drug experience group) rhesus monkeys served as subjects. During baseline, drug-naïve subjects chose between a fixed food amount on one option and increasing food on the other option, and cocaine-experienced subjects chose between the same fixed food amount on one option and increasing cocaine doses (0-0.032 mg/kg/injection) on the other option. During substitution tests, different BZ-type compounds were substituted for the increasing food amounts or cocaine doses. Compounds evaluated included three α1-sparing compounds (i.e., YT-III-31, MP-III-24, and MP-III-80), a nonselective BZ, midazolam, and an α1-preferring compound, zolpidem. The α1-sparing compounds were not self-administered on their own in either group. Somewhat surprisingly, neither was the nonselective compound, midazolam. However, zolpidem was self-administered by both groups. These results suggest that α1-sparing compounds do not function as reinforcers on their own in drug-naïve or cocaine-experienced subjects. From a therapeutic perspective, α1-sparing compounds may hold promise as treatments for anxiety with reduced potential for misuse.

Poster 39

Pharmacokinetics of Aristoquinoline Targeting α3β4 Nicotinic Acetylcholine Receptors for Cocaine Use Disorder

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Cocaine is a highly addictive stimulant, with 1.4 million Americans diagnosed with cocaine use disorder. In 2023, provisional data from the CDC's National Center reported 29,918 cocaine-related deaths in the United States. To date, there are no approved pharmacological treatments for cocaine use disorder, contributing to elevated relapse rates. Recent research highlights α3β4 nicotinic acetylcholine receptor (nAChR) inhibition as a potential therapeutic approach to treat cocaine use disorder. In this perspective, aristoquinoline, an alkaloid from Aristotelia chilensis, emerges as a selective and noncompetitive inhibitor of α3β4 nAChR. It significantly reduces cocaine-seeking behavior in an animal model of relapse, offering hope for improved cocaine use disorder treatment. However, no pharmacokinetic data has been reported in the literature. Therefore, the present research aimed to investigate the in-vitro and in-vivo pharmacokinetics of aristoquinoline utilizing the ultra-performance liquid chromatography-tandem mass spectrometry-based (UPLC-MS/MS) bioanalytical method. Results demonstrated high permeability across human colorectal adenocarcinoma (caco-2) cell monolayer, large volume of distribution, high clearance, and low oral bioavailability in male Sprague Dawley rats. Importantly, aristoquinoline crosses the blood-brain barrier, making it suitable for central nervous system targeting. The study highlights aristoquinoline as a therapeutic candidate targeting α3β4 nAChR for cocaine use disorder, with the ability to cross the blood-brain barrier. However, its rapid metabolism in rat liver microsomes and low oral bioavailability suggests the need to explore active metabolite(s) pharmacodynamically and its administration through non-peroral routes of administration along with advanced formulation strategies for further development.

Poster 40

Discriminative Stimulus Effects of Novel Designer Benzodiazepines

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Aims: The trafficking of "novel designer benzodiazepines" has significantly increased in recent years through online platforms and underground drug markets. According to the 2024 UNODC report, bromazolam and clonazolam have been identified in clinical admissions and post-mortem cases, and have dominated as two of the top 10 drugs in the NPS category. The purpose of this study to evaluate behavioral effects of bromazolam and clonazolam while determining the potency and efficacy of these compounds in comparison to midazolam. Methods: Discriminative stimulus effects of bromazolam and clonazolam were tested in male Sprague-Dawley rats trained to discriminate midazolam (3 mg/kg) from vehicle (0.9% saline). Results: Midazolam (ED50 = 0.25 mg/kg) produced dose-dependent substitution up to the training dose (3 mg/kg). Midazolam significantly increased the response rate when compared to vehicle control (0.9% saline). The drug discrimination assay of bromazolam in rats (ED50 = 0.41mg/kg) yielded full substitution of the discriminative stimulus effects produced by midazolam (ED50 = 0.25 mg/kg). Bromazolam also significantly decreased the response rate when compared to vehicle (10% DMSO/45% DMF/45% DI). The drug discrimination assay of Clonazolam in rats (ED50 = 0.125 mg/kg) yielded full substitution of the discriminative stimulus effects produced by midazolam (ED50 = 0.25 mg/kg).
Conclusion: These results suggest that both bromazolam and clonazolam fully substituted for midazolam in the drug discrimination assay, indicating a potential for abuse similar to that of midazolam. Future studies on locomotor activity could help determine whether the anxiolytic and CNS depressant properties of these novel designer benzodiazepines align with those of midazolam.
Support: Supported by NIDA contract N01DA-23-8936

Poster 41

Investigating Organic Cation Transporter 3 on Serotonergic Neurons in Fear Related Behavior and Serotonin Clearance in Basolateral Amygdala

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Dysfunctional serotonergic (5-HT) neurotransmission is a dominate feature of many neuropsychiatric disorders such as post-traumatic stress disorder and substance use disorder. Treatments for these illnesses often utilize selective 5-HT reuptake inhibitors (SSRIs), which are thought to produce therapeutic effects by raising extracellular 5-HT in key brain regions by blocking the 5-HT transporter (SERT) an uptake-1 high-affinity low-capacity transporter. However, SSRIs have limited treatment efficacy suggesting targeting other 5-HT clearance mechanisms, such as organic cation transporter 3 (OCT3), an uptake-2 low-affinity high-capacity transporter, may serve as adjunct therapy. The basolateral amygdala (BLA), a central hub of anxiety and fear processing, receives dense 5-HT inputs from the dorsal raphe (DR). Since DR neurons express OCT3, we hypothesized that OCT3 located on 5-HT neurons plays a critical role in regulating fear behaviors through clearance of 5-HT in BLA. To test to what extent OCT3 on 5-HT neurons plays a role in fear behaviors and clearance of 5-HT in BLA, we generated a conditional knockdown (KD) of OCT3 on 5-HT neurons by crossing tamoxifen-inducible 5-HT-Cre mice (TPH2-icre/ERT2) with OCT3-floxed mice (OCT3fl/fl). We found that freezing during contextual fear recall was diminished in KD compared to control (mice lacking Cre recombinase). However, this was not related to differences between KD and control mice in clearance of 5-HT from extracellular fluid in BLA across a range of physiologically relevant concentrations. These results suggest that while OCT3 on 5-HT neurons plays a role in fear memory related behaviors, clearance of 5-HT via OCT3 on 5-HT neurons in BLA is likely not a contributing factor.

Poster 42

LSD Treatment Reduces Alcohol Preference in Mice

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Alcohol is the most damaging drug of abuse in terms of mortality, dependence, economic costs, and many other factors1. Despite this, the effects of current treatments for alcohol use disorder (AUD) remain disappointingly small4. Classic psychedelics, such as lysergic acid diethylamide (LSD), have shown promise as a treatment for AUD since the 1960's13. However, due to constraints from the Controlled Substances Act, clinical trials with psychedelics have preceded much preclinical research. Therefore, little is known about the mechanisms by which a single dose of LSD could produce improvements in AUD. This study thus aims to 1) determine whether LSD-induced reduction in alcohol preference is cumulative, and 2) whether the hallucinogenic effects of LSD are necessary for its impact on alcohol preference. To test this, 25 adult, male fosTRAP2xAi14 mice were given free access to 20% ethanol in drinking water 5 days/week for 4 weeks. Following exposure, mice were injected i.p. with either saline, LSD 50ug/kg, or BOL-148 3mg/kg. After 10 minutes, animals were given access to both water and 20% ethanol solution for 4 weeks to test alcohol preference, with a second injection given at 2 weeks. Results showed a main effect of treatment [$F(2,25)=3.50$, $p=0.046$], with a reduction in ethanol consumption in LSD- vs saline-treated mice ($p=0.049$) but not in BOL- vs saline-treated mice ($p=0.877$). There was a similar effect of treatment for ethanol preference [$F(2,25)=7.41$, $p=0.003$], with a reduction in preference in LSD- vs saline-treated mice ($p<0.001$) and a non-significant reduction in BOL- vs saline-treated mice ($p=0.064$). Ethanol preference was not reduced in LSD-treated mice from week 1 follow-up to week 3 ($p=0.726$) but was reduced in BOL-treated mice ($p=0.004$). These results support a significant, nonadditive effect of LSD on alcohol preference, as well as a modest, additive effect of a non-hallucinogenic LSD analog.

Poster 43

Locomotor and Discriminative Stimulus Effects of Five Synthetic Cathinones

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Aims: Synthetic cathinones are synthesized as legal alternatives to methamphetamine (meth), cocaine, and MDMA and can produce serious health risks. The DEA identified five synthetic cathinones of interest: N-ethylpentedrone, N-ethylheptedrone, N-butylhexedrone, 4-methylpentedrone, and 4-MEAP. These compounds were tested to determine their locomotor stimulant and psychostimulant-like discriminative stimulus effects.
Methods: Locomotor activity was tested in male Swiss-Webster mice to identify behaviorally active dose ranges and time courses. Discriminative stimulus effects of five synthetic cathinone's were tested in male Sprague-Dawley rats trained to discriminate cocaine (10 mg/kg, 10-min pretreatment) or meth (1 mg/kg, 10-min pretreatment) from saline vehicle.
Results: Three compounds produced locomotor stimulant phases: N-ethylpentedrone (ED50= 3.8 mg/kg), N-ethylheptedrone (ED50= 10.4 mg/kg), and 4-MEAP (ED50= 1.87 mg/kg). N-butylhexedrone (ED50= 84.3 mg/kg) and 4-methylpentedrone (ED50= 19.5 mg/kg) produced a depressant phase. N-ethylpentedrone and N-ethylheptedrone substituted for discriminative stimulus effects produced by meth and cocaine. 4-MEAP fully substituted for meth only, 4-methylpentedrone partially substituted for meth and fully substituted for cocaine.
Conclusions: Three of the compounds, N-ethylpentedrone, N-ethylheptedrone, and 4- MEAP produced stimulant effects in LMA and fully substituted for cocaine and meth. This suggests they could be used as cocaine or meth substitutes. 4-Methylpentedrone partially substituted for cocaine and failed to substitute for meth, showing low abuse liability compared to meth or cocaine. N-butylhexedrone was a depressant effect and partially substituted for cocaine in DD. This compound also produced writhing which could cause stomach distress in humans, lessening its abuse liability.
Support: Supported by NIDA contract N01DA-18-8936

Poster 44

Social enhancement of cocaine intake: Role of reinforcing stimulus

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One of the leading prognosticators of whether an adolescent or young adult will use drugs is whether the person's friends use drugs. Preclinical studies report that cocaine intake increases in the presence of a social partner that is also self-administering cocaine, but it is not known whether this effect extends across reinforcers. The objective of this study was to examine the role of the reinforcing stimulus in the effects of social contact on cocaine self-administration. To this end, male and female Long-Evans rats were implanted with intravenous catheters and trained to self-administer cocaine or a semi-solid palatable food (i.e., cake icing) on a fixed ratio (FR1) schedule of reinforcement. All tests were conducted in custom-built operant conditioning chambers that allowed two rats to simultaneously self-administer either cocaine or food while maintaining complete visual, auditory, and olfactory contact with a social partner. In rats self-administering cocaine, cocaine intake was significantly greater when a partner was also self-administering cocaine relative to when a partner was self-administering food or when a partner was responding under extinction (i.e., no cocaine or food was available). In rats self-administering food, food intake was significantly greater when a partner was also self-administering food relative to when a partner was self-administering cocaine. These data indicate that social learning processes influencing drug use depend on the reinforcer maintaining the behavior of both the individual and the individual's social partner.

Poster 45

Repeated High-Dose Amphetamine Leads to a Long-Term Decrease in the Sign-Tracking-to-Goal-Tracking Ratio with Compound Lever-Light Cues but Not with Lever-Alone Cues.

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Prior psychostimulant use is linked to cognitive and motivational abnormalities in humans, and animal research helps explore this relationship. One focus is how psychostimulant exposure influences behavior in AutoShaping, where sign-tracking refers to responses to a reward-predictive cue, while goal-tracking refers to responses toward the site of reward delivery. Research suggests that prior psychostimulant exposure may reduce sign-tracking to complex cues (e.g., compound lever-light) but increase sign-tracking to simpler cues (e.g., lever-only). We hypothesized that amphetamine exposure would reduce the sign-tracking-to-goal-tracking ratio for complex cues but not for simple cues. Fifty-eight Sprague-Dawley rats (males and females) were randomly assigned to receive 4 mg/kg of amphetamine or saline (i.p.) for seven consecutive days. Behavioral testing began 14 days post-exposure, assessing sign-tracking and goal-tracking with lever-alone and compound lever-light cues. A mixed factor ANOVA revealed a significant reduction in the sign-tracking-to-goal-tracking ratio for compound cues ($p < .05$), but no significant effect for lever-alone cues. However, amphetamine did not significantly alter the response rates of sign-tracking or goal-tracking behaviors. These findings suggest that cue complexity modulates the long-term effects of psychostimulant exposure on reward-related learning, contributing to our understanding of addiction-related behaviors.

Poster 46

Sex Comparisons of the Effects of Gabapentin on the Expression of Morphine Withdrawal in Rats

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Gabapentin is widely used off-label to treat opioid withdrawal. However, the effectiveness of gabapentin in attenuating opioid withdrawal and any potential sex difference in those interactions has not been rigorously examined. This study compared the ability of gabapentin to attenuate the expression of morphine withdrawal in 14 groups of rats (7 treatment groups A-G x 2 sex groups; N=8/condition). Morphine dependence was established by administering escalating doses of morphine (10-40 mg/kg, s.c.) b.i.d. (7 AM and 5 PM, Days 1-4) in Groups A-D, while Groups E-G received saline. At 7 AM and 5 PM on Day 5, Groups A-D received 40 mg/kg morphine and saline, respectively, while Groups E-G received saline. Subsequently, Group A, the morphine-dependent control group, received saline (7 AM), and groups B-G received gabapentin (32, 100, or 320 mg/kg, s.c., 7 AM). Starting on Day 6, morphine withdrawal (body weight loss and 14 somatic withdrawal signs) was assessed at 7 AM daily. Rotarod performance was also measured. Gabapentin attenuated body weight loss in females but not males. In males, all doses of gabapentin reduced withdrawal signs (e.g., diarrhea and vocalization) from 9 to 3 on Day 1. Attenuation of withdrawal signs did not appear to be due to non-specific behavioral disruption because no dose of gabapentin significantly decreased rotarod performance. In females, Group A did not exhibit significant withdrawal signs but enhanced rotarod performance that was fully reversed by gabapentin. These results suggest sex differences in the ability of morphine to express its withdrawal and gabapentin to attenuate the expression of morphine withdrawal. Supported by USPHS grants R01DA058018 and R25DK113659 (the STEP-UP HS program), and the Welch Foundation (Grant AQ-0039).

Poster 47

Dual-Target μ-Opioid (MOR)/Dopamine D3 (D3R) Receptor Ligands Based on Etonitazene

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The development of opioid analgesics that mitigate acute and/or chronic pain, without eliciting common adverse effects, such as euphoria, respiratory depression, and addiction, remains a significant and complex challenge in medication discovery. Opioid analgesics exert their effects primarily through activation of opioid receptors in the central nervous system (CNS), including the mu (MOR), delta (DOR), and kappa (KOR) opioid receptors. Among these, MOR agonists are the most potent pain relievers; however, they are also associated with significant side effects, including addiction potential. To address these challenges, our laboratory is investigating a dual-target ligand strategy, using a bivalent drug design approach by combining the primary pharmacophore (PP) of a MOR agonist with the PP of a dopamine D3 receptor (D3R) antagonist/partial agonist. This approach aims to modulate the reward-related behaviors typically induced by MOR activation, potentially reducing the risk of abuse while maintaining analgesic efficacy. We selected etonitazene, a potent MOR full agonist (MOR Ki=0.149 nM), as the structural template. We modified etonitazene by incorporating various D3R pharmacophores with varying linking chains to create a series of novel compounds. In our initial series of N-substituted etonitazene analogs, we identified three lead candidates: KJ02-44 (MOR Ki=33.4 nM; D3R Ki=90.6 nM), KJ02-54 (MOR Ki=29.7 nM; D3R Ki=53.8 nM) and KJ02-55 (MOR Ki=89.6 nM; D3R Ki=45.4 nM) based on their nearly equipotent binding affinities for both MOR and D3R, while etonitazene is inactive at D2-like receptors up to 100 μM. Bioluminescent Resonance Energy Transfer (BRET) assays confirmed that all three compounds function as MOR agonists and either D3R antagonists or partial agonists. Notably, KJ02-44 exhibited the most favorable profile, displaying high stability in both mouse and rat microsomal metabolism assays up to 60 min. When tested in C57BL/6J male mice, KJ02-44 demonstrated analgesic effects, achieving maximal latency in the hot plate assay at a dose of 100 mg/kg (s.c.). In comparison, KJ02-54 and KJ02-55 showed only partial analgesic effects at that dose, possibly due to rapid metabolism. Moreover, KJ02-44 showed analgesic efficacy with limited motor stimulation, potentially indicative of a lower risk for abuse. Further studies are warranted to validate these preliminary results.

Poster 48

The Locomotor and Discriminative Stimulus Effects of N-Cyclohexyl Butylone & N-Cyclohexylmethylone

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Rationale: N-cyclohexyl butylone and N-cyclohexylmethylone are cathinones found on the street that produce substantial morbidity and mortality but are not explicitly scheduled yet. Hypothesis: Both test compounds will produce psychoactive effects similar to methamphetamine (Meth), cocaine (Coc) and/or 3,4 methylenedioxymethamphetamine (MDMA). Methods: N-cyclohexyl butylone and N-cyclohexylmethylone were each tested for their ability to stimulate locomotor activity (LMA) in male Swiss-Webster mice and to substitute for the discriminative stimulus effects of Meth (1 mg/kg), Coc (10 mg/kg) or MDMA (1.5 mg/kg) in male Sprague-Dawley rats. Results: N-cyclohexyl butylone produced dose- and time-dependent stimulation of LMA (ED50=2.80 mg/kg) lasting 160 min. The relative efficacy of N-cyclohexyl butylone to Meth was 73%. In contrast, N-cyclohexylmethylone depressed LMA following 1 and 2.5 mg/kg (from 60 to 90 min), and stimulated LMA following 5 mg/kg (from 10 to 30 min). Higher doses (10 – 50 mg/kg) produced no significant effects. The relative efficacy of N-cyclohexylmethylone to Meth was 68%. N-Cyclohexyl butylone fully substituted for the discriminative stimulus effects of Meth (ED50=9.85 mg/kg) and Coc (ED50 =11.56 mg/kg). N-cyclohexylmethylone partially substituted for the effects of Meth at 5 and 10 mg/kg (45 ± 17% and 55 ± 17%) and produced convulsions (1 of 9 rats). N-cyclohexylmethylone (tested from 2.5 to 5 mg/kg) failed to substitute for Coc. Both compounds failed to substitute for MDMA up to doses that suppressed responding. Conclusions: N-cyclohexyl butylone will likely have similar abuse liability as Meth and Coc. N-cyclohexylmethylone has weak, delayed stimulant effects, and will likely have much less abuse liability but may be more dangerous due to the convulsant effects at a dose (10 mg/kg) that partially substituted. Neither of the compounds were MDMA-like.

Poster 49

Differential Rearing and Biological Sex Alters the Efficacy of 2,5-dimethoxy-4-iodoamphetamine (DOI) during Sucrose Self-administration

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Adverse Childhood Experiences (ACEs) can lead to compulsive behaviors and elevated reward-seeking which are modulated by serotonergic (5-HT) transmission. The 5HT2A receptor (5-HT2AR) has emerged as a therapeutic candidate for treating compulsive disorders; however, ACEs negatively impact 5-HT and 5-HT2AR suggesting therapeutic efficacy may be worse in these populations. To examine these influences, we utilized an animal model of ACEs coupled with sucrose self-administration. Male (n=16) and female (n=16) Sprague-Dawley rats were reared in enriched or isolated environments for 30 days before acquiring sucrose-self-administration in daily 30-minute sessions. Once stabilize on FR5, rats were treated with saline or 2,5-dimethoxy-4-iodoamphetamine (DOI, 0.03, 0.065, 0.1, 0.3 mg/kg; s.c.), a preferential 5-HT2AR agonist, in a counterbalanced within-subject design and tested in the FR5 sucrose self-administration procedure. Following the DOI dose-response, rats were trained under extinction conditions and tested in cue-induced reinstatement. On the final extinction day, rats received either saline or the effective dose of DOI (0.3 mg/kg; s.c) and then the opposite treatment during reinstatement testing. Results indicated a significant three-way interaction between rearing environment x DOI dose x biological sex on active lever presses and total sucrose pellets. Further analysis revealed female EC and IC rats were different following 0.065 and 0.3 mg/kg DOI, while male EC and IC rats were different following 0.3 mg/kg DOI. Inactive lever presses were unaffected following DOI treatment. In conclusion, developmental manipulations influence the efficacy of DOI and needs to be considered when interpreting preclinical experiments and hallucinogenic therapeutics reward and motivational disorders.

Poster 50

Tackling the cyclical connection between PTSD and OUD: Traumatic stress enhances risk-based decision-making in rats.

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The prevalence of Post-Traumatic Stress Disorder (PTSD) in patients with Opioid Use Disorder (OUD) ranges up to 50% in the clinical setting and treatments for this co-morbid condition remain ineffective. Both PTSD and OUD are independently associated with impairments in decision making; thus, it is possible that altered decision making may contribute to their comorbidity. To explore this possibility, this study investigated the casual role of traumatic stress on risk-based decision making in a rodent model. Sixteen Long-Evans rats (n=8/sex) were trained on the Risky Decision-Making Task (RDT), in which rats chose between two levers. A press on the small, safe lever resulted in the delivery of a small food reward, whereas a press on the large, risky lever delivered a large food reward associated with an increasing probability of footshock punishment. The 60-minute task was comprised of 5 blocks, each consisting of 10 free-choice trials. Footshock probability increased in increments of 25% (0, 25, 50, 75, 100%). Once stable behavior on the RDT was achieved, rats were assigned to the “stressed” or “non-stressed” group. In Context A, “stressed” rats received 15, 1 mA footshocks; “non-stressed” rats were placed in the same context but did not receive footshocks. One day later, both groups received a mild stressor (one 1mA footshock) in Context B and were tested for stress-enhanced fear learning 24 h later in Context B. Time spent freezing was measured as a proxy for fear learning. Rats were then re-tested on the RDT. “Stressed” rats froze significantly more than “non-stressed” rats after the mild stressor, demonstrating stress-enhanced fear learning. Additionally, following the stress experience, “stressed” rats chose the large, risky lever significantly more than baseline choice behavior. Understanding the complex relationship between traumatic stress and decision making is critical for developing targeted therapies for treating the comorbidity between PTSD and OUD.

Poster 51

A Novel Strategy For Identifying Structural Features Of Molecules Critical For Blood-Brain Barrier Penetration for Substance Use Disorder Therapeutics

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The blood-brain barrier (BBB) is a critical physiological structure that regulates molecular transport between the blood and brain, thereby maintaining central nervous system homeostasis. Comprising a sealed endothelial membrane supported by various cellular components, the BBB's selective permeability poses a significant challenge for neuropharmacology, particularly in developing treatments for substance use disorders (SUDs). Many potential therapeutic agents for SUDs fail to cross the BBB, limiting their efficacy in targeting key brain regions involved in addiction and dependence. This research strategy explores a novel approach for identifying molecular fingerprints in compounds that cross the BBB to elucidate specific electronic-structural features that are characteristics of the BBB-crossing compounds. These fingerprints are atom pairs with specific electronic and structural features characterized by nuclear magnetic resonance (NMR) chemical shifts and interatomic distances. The research has three specific aims: (1) identify and characterize molecular fingerprints of BBB-penetrating compounds, (2) analyze and cluster BBB-penetrating compounds based on molecular fingerprints, and (3) validate the predictive power of the molecular fingerprint approach. This study utilizes quantum chemistry for NMR shift calculations and molecular structure optimization. Molecules are clustered using reproducible fingerprints and correlated with their metabolic functions and tissue distribution. This research can accelerate SUD therapeutics development by enabling the design of compounds that effectively cross the BBB and target key neurobiological pathways involved in addiction and withdrawal.

Poster 52

The Effects of Mitragynine on Methamphetamine Self-Administration in Rats Under a Progressive Ratio Schedule

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In recent years, Mitragyna speciosa (kratom) has gained attention for its potential as an alternative medicine for substance use disorders (SUD). This study evaluated the effects of mitragynine on methamphetamine self-administration using a progressive ratio (PR) schedule of reinforcement. This study builds upon a previous experiment where mitragynine showed no significant impact on food reinforcement under PR schedule. In the current study, male and female Sprague Dawley rats were implanted with jugular catheters and trained to self-administer methamphetamine (0.032 mg/kg/infusion) intravenously under a fixed ratio (FR) 1 schedule, with the ratio gradually increasing to FR5. Once stable responding was established, rats were transitioned to a PR schedule to measure motivation, with the breakpoint serving as the primary outcome. Afterward, rats were pretreated with either vehicle or mitragynine (10, 17.8, 32, 56 mg/kg, i.p.), with the order of doses counterbalanced. Results showed that methamphetamine self-administration led to significant lever pressing on the active lever. Mitragynine significantly reduced the breakpoint, indicating an attenuation in motivation for methamphetamine. These findings suggest that mitragynine may reduce methamphetamine self-administration. Unlike the food reinforcement experiment, where no significant effects were observed, mitragynine demonstrated an ability to attenuate motivation for methamphetamine self-administration.

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Poster 53

Global Changes in Gene Expression in Brain Micro-Vessels in a Mouse Model of Alcohol Dependence

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Alcohol (ethanol) use disorder (AUD) is a chronic, relapsing brain disease. Recent evidence suggests that brain microvasculature cells may contribute to the development of AUD. We hypothesize chronic ethanol exposure alters micro-vessel gene expression and Endothelial Cell (EC) neuroimmune functions, contributing to increased ethanol consumption and AUD development. We used a high voluntary ethanol drinking mouse model by crossing ethanol-naïve FVB/NJ females with C57BL/6J males, generating FVB/B6J F1 hybrids. Animals were exposed to chronic intermittent ethanol (CIE) vapor by exposing mice to either ethanol vapor or air to model ethanol dependence. Microvessels were enriched from the frontal cortex after final vapor. We performed bioinformatics analysis to identify differentially expressed genes (DEGs) as well as over-represented functional groups and cell types. In females, microvessels were more responsive to ethanol exposure than in males (1,062 and 112 DEGs, respectively). This analysis revealed immune-related DEGs downregulated in females including Ccl5, Cd8a, and H2-T23. In contrast, male microvessel DEGs demonstrated an upregulation of antiviral-related genes, including Irf7 and Oas2. Cell type-specific overrepresentation analysis utilized molecular markers from human single-nucleus RNA-Seq databases for both human brain vasculature and Peripheral Blood Mononuclear layer cells (PBMCs). For example, in females, we observed a significant over-representation of venous ECs and venous, capillary, and arterial ECs in males. Within the PBMC analysis, we identified several over-represented T-cell populations, including Cd8+ effector memory (TEM) among downregulated DEGs in females. Taken together, these data further our understanding of the neuroimmune mechanisms of the brain vasculature potentially contributing to excessive ethanol consumption. Funding provided by R01AA27096 to IP, AHA 24PRE1184797 to BRK.

Poster 54

Inhibition of Orexin-1 Receptors Attenuates Morphine-associated reward and neurobiological alterations.

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Strong activation of the brain's reward circuitry by morphine drives the progression toward morphine abuse. Additionally, morphine stimulates orexin neurons in the lateral hypothalamus (LH), which are integral to reward processing. The orexin system, particularly the orexin-1 receptor (OrxR1), is implicated in mediating reward-seeking behaviors. While orexins are known to play a key role in reward behaviors, the specific contribution of OrxR1 to morphine-associated reward remains unclear, particularly regarding potential sex differences in orexin-morphine interactions. This study examined the effects of the OrxR1 antagonist SB334867 on morphine-induced conditioning place preference (CPP) in male and female rats to assess OrxR1 role in morphine reward and potential sex-dependent differences. Thus, the goal of the present study was to investigate whether the OrxR1 antagonist SB334867 reduces morphine induced CPP. 23 adult male and female Long Evans rats underwent a seven-day morphine CPP paradigm. Over five conditioning days, rats were administered SB334867 (30 mg/kg, IP) 30 minutes prior to morphine (10 mg/kg, SC). CPP expression was assessed 24 hours post-conditioning, followed by transcardial perfusion. Whole brains were extracted, and coronal slices from the PFC, LH, VTA, NAc, DS, and hypothalamus were processed for double-label IHC to examine c-Fos and orexin co-expression. Results demonstrate that both male and female rats in the control group developed morphine CPP. Pre-treatment with SB334867 during morphine conditioning attenuated morphine induced CPP. Additionally, c-Fos expression in morphine-treated animals was attenuated by SB334867, specifically in orexin receptor-expressing cells of the lateral hypothalamus (LH). In conclusion, blocking OrxR1 during morphine conditioning significantly reduced morphine induced CPP. Reduced c-Fos expression in orexin-receptor expressing LH neurons, suggests disruption of reward-related circuits.

Poster 55

Synergistic Effects of Pre-Conception Dual-Parent Alcohol Exposure on Adult Offspring Drinking/Compulsive Behaviors and Locomotor Activity

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While a breadth of research has demonstrated that prenatal maternal alcohol exposure can produce lifelong neurodevelopmental/behavioral disorders in offspring, the consequences of paternal alcohol consumption are often overlooked in preclinical studies. Given the prevalence of shared drinking behaviors in couples, this study investigates whether dual-parent alcohol exposures impose distinct offspring behavioral outcomes compared to single-parent alcohol exposures. Before breeding, adult C57BL/6J mice received either water (controls) or alcohol (10% ethanol) using the Drinking-in-the-Dark paradigm. Sires were exposed for two spermatogenic cycles (70 days), while dams were exposed for 10 days before & after conception. Adult offspring (P200+) then underwent: a) operant chamber self-administration tests for alcohol-seeking behaviors, b) an Open-Field (OF) test for locomotor activity, & c) marble-burying tests for compulsive behaviors. Our preliminary results indicate that dual-parent exposure significantly increased ethanol consumption compared to single-parent exposure under fixed & progressive ratio administration protocols, and increased abstinence-induced ethanol consumption compared to maternal exposure-alone. Dual-parent exposure didn't augment time in the OF center or average speed traveled by single-parent exposures. Finally, dual-parent exposure increased the number of marbles buried in marble-burying tests compared to maternal exposure-alone. We are currently performing a fully-powered replication study to confirm the synergistic effects of dual-parent alcohol exposure on offspring behaviors & to determine whether offspring behavioral outcomes differ between sons and daughters.

Poster 56

Effects of Antisocial Personality Traits on Marijuana Use Patterns in At-Risk Adolescents

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Previous research has demonstrated a positive relationship between antisocial traits and substance abuse among adolescents (Bates & Labouvie, 1995; Wood et al., 1995). This study evaluates how antisocial traits may be associated with the severity and frequency of marijuana use in a sample of at-risk adolescents (N = 100; Mage = 16.74) enrolled in a military-style, residential program.

This sample is predominantly male (76.6%) and Caucasian (59.8%). Antisocial traits were assessed using the antisocial subscale from the Personality Assessment Inventory – Adolescent (PAI-A; Morey et al., 2007). Marijuana use patterns were assessed using items from the Youth Risk Behavior Survey (YRBS; CDC). Analyses revealed significant positive associations between antisocial traits (ANT) and several marijuana-use variables, including total times used, frequency of use, and consequences experienced from use. These correlations suggest that higher levels of antisocial traits are associated with more problematic marijuana use patterns. Additionally, a negative correlation was found between ANT and age at first use, indicating that individuals with higher antisocial traits tended to initiate marijuana use at a younger age. Statistical analyses showed highly significant one-sided p-values ($p < .001$) for the relationships between antisocial traits and marijuana use variables (TANT).

Screening for antisocial traits may help identify adolescents at highest risk for developing problematic marijuana use patterns. Future research should explore the specific mechanisms by which antisocial traits contribute to problematic patterns of marijuana use.

Poster 57

Respiratory Depressant Interactions of Fentanyl and Xylazine and Their Reversal by Naloxone and Yohimbine in Mice

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Background: Misuse of fentanyl, a mu opioid receptor (MOR) agonist, remains a major U.S. health crisis. Fentanyl is increasingly adulterated with xylazine, a veterinary sedative and alpha-2 adrenergic receptor (α2AR) agonist, and the mixture is colloquially referred to as "tranq dope". In 2022, xylazine contributed to 11% of overdose cases, prompting the DEA to label it as an exacerbating factor in the fentanyl crisis. Overdoses involving xylazine may be more refractory to reversal by naloxone, a MOR antagonist. This study investigated the respiratory depressant effects of fentanyl, xylazine, or their combination and whether these effects could be reversed by naloxone, yohimbine (α2AR antagonist) or their combination. Methods: Male C57Bl/6J mice were tested using whole-body plethysmography. Dose-response and time-course determinations were performed for fentanyl and xylazine. A respiratory depressant dose of each agonist was selected for combination testing and antagonist reversal studies. Minute volume (MVb), and its components, tidal volume (TVb) and frequency (Freq), were recorded and analyzed using 2-way ANOVA and Holm-Sidak post-hoc tests. Results: Fentanyl decreased MVb by reducing Freq and increasing TVb, and naloxone, but not yohimbine, reversed these effects. Xylazine reduced MVb by lowering both TVb and Freq, and yohimbine reversed these effects. "Tranq dope" decreased MVb by reducing Freq and increasing TVb, and naloxone, but not yohimbine reversed these effects. Interestingly, the combination of antagonists caused a more rapid reversal than naloxone alone. Conclusions: Fentanyl and xylazine decreased respiration that was reversed by appropriate receptor-selective antagonists. Furthermore, α2AR antagonists may have potential as an adjunct to naloxone for quicker reversal of "tranq dope" overdose and thus may mitigate risk of hypoxia.

Poster 58

The effect of omitting pre-session enrichment on dose-response and demand curves of rats self-administering fentanyl

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In recent years, we developed a way to monitor frustration-related behavior by measuring duration of bar pressing during operant tasks. Though average duration of bar pressing reliably increases in response to operant frustration programs like extinction, whether duration of pressing is also sensitive to external frustration is not known. To address this, we trained adult rats to self-administer fentanyl daily immediately following 30 minutes of environmental enrichment (EE). On test days, EE was omitted and rats were placed directly into self-administration. The number of infusions obtained for each dose was recorded and bar press durations were monitored. Dose-response curves were generated and then converted into BE demand curves to assess substance use disorder-related phenotypes. We hypothesized that duration of pressing and drug-taking would both increase. However, we found that during omission days, rats exhibited a significant right-ward shift in the ascending limb of a dose-response curve, taking fewer fentanyl infusions for doses 7-9. This contradicts our hypothesis and previous research showing that rats reared in enriched conditions (EC) exhibit addiction-resilient phenotypes in both DRC and BE analyses. Moreover, there was no effect on duration of pressing. Further experimentation is required to make conclusive claims on what these findings mean.

Poster 59

Treatment with psilocybin counteracts cognitive decline in aged mice

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An estimated 40% of individuals will experience some cognitive decline after the age of 65. Although most pharmaceutical research to date has focused on drug development to prevent or treat dementia, interest is growing in utilizing classic psychedelic drugs, such as psilocybin, as a potential therapy for age-related cognitive decline. These drugs have shown a well-characterized ability to increase neuroplasticity and induce acute therapeutic effects that last beyond drug elimination, lending them as a promising novel therapy. Though recent preclinical studies have demonstrated both the anxiolytic and antianhedonic effects of these drugs, their impact on age-related cognitive outcomes has not yet been researched. This study seeks to test the hypothesis that psilocybin treatment will reduce symptoms of cognitive aging in aged mice. C57BL/6 mice were group-housed on a reverse light cycle and given food ad libitum (N=78, 47% female; 11-13 months of age). Animals were injected with either 1mg/kg of psilocybin or saline 1/week for 2 weeks. Three days post-injection, animals performed a habituation and three test trials of a water Y-Maze task over four days. Preliminary results show that psilocybin treatment did not affect female mice's cycling (they cycled regularly throughout the duration of the study) or body weights ($F(1,154)= 0.083$, $p= 0.77$, NS). Furthermore, males outweighed females ($F(1,154)= 32.005$, p.

Poster 60

Zolmitriptan, a 5-HT1B/1D receptor agonist, reduces the acquisition of methamphetamine preference in male, but not female adolescent rats.

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Adolescent use of methamphetamine (METH) leads to poor treatment outcomes later in life, and currently, there are no FDA-approved medications for the treatment of METH use disorder. Previous studies showed that activating serotonin 5-HT1B receptors reduces METH-induced conditioned place preference (CPP) expression in adult mice, but the effects of activating 5-HT1B receptors on the acquisition of METH CPP or adolescent rats have not been investigated. Therefore, the present study examined the effect of zolmitriptan, a 5-HT1B/1D receptor agonist, on METH preference in adolescent male and female rats using a 10-day CPP procedure. On baseline (day 1), rats had free access to both sides of a two-sided apparatus for 20 min to assess their preferred and non-preferred sides. During conditioning (days 2-9), rats were injected on alternating days with METH (0, 0.125, 0.25, 0.5, 1.0 mg/kg, intraperitoneally) or saline and were immediately confined to their non-preferred or preferred side for 30 min, respectively. During METH conditioning days, rats received pretreatment of zolmitriptan (0 or 10 mg/kg, subcutaneously) 15 min before METH. On testing (day 10), rats were given free access to both sides of the two-sided apparatus for 20 min to assess their final side preference. Results indicated that zolmitriptan reduced the rewarding effects of METH in male, but not female adolescent rats. Overall, the findings highlight sex differences in the role of 5-HT1B receptors in METH reward across development and that this receptor system is a viable pharmacological target for the treatment of METH use disorder.

Poster 61

Effects of the monoacylglycerol lipase inhibitor MJN110 on mechanical hyperalgesia and the affective components of inflammatory pain in male and female rats

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In recent years, extensive research has been conducted to find non-opioid based analgesics. Cannabinoids have proven to be effective antinociceptive agents in preclinical rodent models, but their use in humans is not well supported. Most clinical studies demonstrate a low to moderate effect, or even hyperalgesia. There are some indications however, that cannabinoids may play a role in the affective dimension of pain, in which mood and emotions can influence the perception of pain. Here we explored the use of a novel monoacylglycerol lipase (MAGL) inhibitor, MJN110, in alleviating chronic inflammatory pain induced by complete Freund's adjuvant (CFA) injections in the hind paw. MAGL is the primary enzyme that degrades 2-arachidonylglycerol (2-AG) which is an endocannabinoid produced in the CNS. MJN110 increases 2-AG concentrations with complete inhibition of MAGL at 5 mg/kg in rodents. In our model MJN110 dose-dependently (1, 2.5, 5.0 mg/kg, i.p.) increased the paw withdrawal threshold in the CFA-injected hind paw of rats mechanically stimulated with von Frey filaments. This antinociceptive effect was reversed by a subthreshold dose of the CB1 receptor inverse agonist rimonabant (SR141716A, 0.3 mg/kg i.p.), indicating that the MJN110-induced antinociception is CB1 receptor mediated. We then tested the MJN110 in the place escape avoidance paradigm (PEAP) which models some aspects of pain affect. Rats are placed in a chamber with a white or black side and a mesh floor. Every 15 seconds either the CFA-injected (painful) paw is poked on the black side or the non-painful paw is poked if the rat is on the white side. Over the 30 min session the rats learn to avoid the preferred black side. Pretreatment with an antinociceptive drug blocks this learned escape behavior resulting in rats spending more time in the black side of the chamber than vehicle treated rats.

Poster 62

Effects of early-life environment on frustration and motivation

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The role of environmental enrichment (EE) in mediating protective phenotypes of seeking and taking of natural and drug rewards has been extensively demonstrated. However, little progress has been made in determining the factors underlying this phenomenon that could be targeted for therapeutic development against substance use disorders. Recent advancements in behavioral neuroscience have enabled us to measure frustration-related behavior simultaneously with motivation-related behavior by monitoring duration of bar pressing in addition to frequency of bar pressing. In the current study, we leverage this to understand how frustration may mediate the protective functions of EE. We used12 rats reared in EE and 12 rats reared in isolation to compare their motivation- and frustration-related operant behavior for sucrose. Interestingly, EE rats demonstrate higher baseline bar press durations at FR1, suggesting increased baseline frustration-related behavior. Additionally, EE rats take fewer reinforcements during FR1 and EXT, consistent with increased frustration. Despite baseline differences in average duration of bar pressing, however, we find that both groups exhibit similar increases in duration of bar pressing relative to their corresponding FR1 sessions. Together, this evidence points toward a modified frustration-motivation interface in isolated animals compared to enriched animals. Though both groups exhibit similar frustration-related behavior, the isolated group is willing to tolerate frustration for longer to obtain rewards, indicating a weaker ability for frustration to dampen motivation-based susceptibility. These rats are currently being assessed for cocaine self-administration, and these data will provide a better picture regarding the role of emotionality and environment.

Poster 63

Characterizing the interactions of fentanyl and xylazine on food-reinforced behavior in rhesus monkeys

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The opioid crisis remains a major public health challenge, with approximately 70% of the 107,000 drug overdose fatalities reported in 2023 involving the synthetic opioid, fentanyl. Recently, the DEA has reported a large percentage of drug seizures of fentanyl also contained xylazine, a non-opioid sedative. According to anecdotal reports from clinicians and people who use opioids, xylazine appears to enhance some abuse- and overdose-related effects of fentanyl, but the behavioral and physiological effects of fentanyl/xylazine mixtures have not been well characterized. This study employs operant food-reinforced behavior in 4 male and 4 female rhesus macaques to determine the nature of the interaction between fentanyl and xylazine. Monkeys responded under a fixed-ratio 20 schedule of sucrose pellet delivery. Response periods occurred every 30 min for up to 3 hr. after subcutaneous administration of fentanyl (0.0056-0.178 mg/kg) or xylazine (0.32-3.2 mg/kg); tests with drug mixtures are pending. Response rate was plotted as a function of time to examine the duration of effect at each dose, and dose-effect curves were determined individually for each monkey. Fentanyl and xylazine reduced food-reinforced responding in a dose- and time-dependent manner, with fentanyl being on average, at least 30 times more potent than xylazine. The potency of each drug to decrease response rate will be used to construct dose mixtures to be tested in each monkey, and the nature of the interaction will be determined using principles of dose equivalence and dose addition. This study provides important context for subsequent studies investigating reinforcing, discriminative-stimulus and ventilatory-depressant effects of xylazine/opioid mixtures. Supported by the NIH (R01DA060215 [DRM] and T32DA031115 [PAM]).

Poster 64

Striatal enkephalin mediates cocaine-induced GABA suppression from D2-MSNs to the ventral pallidum to disinhibit ventral pallidum neurons

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Withdrawal from cocaine self-administration suppresses GABA release from striatal D2-expressing medium spiny neurons (D2-MSNs) to the ventral pallidum (VP), and inhibition of this circuit induces relapse to cocaine seeking. This GABA suppression is reversed by opioid receptor antagonists, suggesting cocaine increases levels of an opioid peptide to affect circuit plasticity. However, the identity and source of the opioid peptide responsible is unknown. We previously showed withdrawal from long-term cocaine increases striatal Penk levels, the gene encoding the opioid peptide enkephalin. We hypothesized cocaine withdrawal increases striatal enkephalin, which acts on presynaptic opioid receptors to inhibit D2-MSN-to-VP and ultimately disinhibit VP neurons. To test this, we used mice lacking Penk from D2-MSNs (D2Penk-KO, n=37) and Adora2a-Cre controls (n=51) and performed ex vivo electrophysiological recordings after withdrawal from long-term cocaine or saline. We found that cocaine withdrawal did not suppress D2-MSN-to-VP GABA in D2Penk-KOs (3W RMANOVA), indicating cocaine acts via striatal enkephalin to suppress GABA transmission in this circuit. Bath application of met-enkephalin suppressed GABA release at D2-MSN-to-VP synapse in all groups, except in cocaine-treated Adora2a-Cre controls, suggesting GABA was already suppressed by heightened tone of endogenous enkephalin (3W RMANOVA). Additionally, inducing GABA release from D2-MSNs inhibited VP neuron firing in saline-treated, but not cocaine-treated, Adora2a-Cre controls (3W RMANOVA), suggesting D2-MSN GABA regulates VP neuron firing, and cocaine-withdrawal suppresses this circuit to disinhibit the VP. These data implicate cocaine-heightened striatal enkephalin as an important mechanism in regulating circuits known to facilitate cocaine seeking.

Poster 65

Positive and Negative Parenting Practices Associated with Adolescent Substance Use

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Involved, warm parenting is positively associated with the development of emotion regulation and impulse control during adolescence, factors which may reduce risk for developing substance use disorders (Morris et al., 2017, Patock-Peckham & Morgan-Lopez, 2006). However, there is limited research directly on the associations between parenting during childhood and drug and alcohol use among adolescents. The current study includes 153 at-risk adolescents (Mage = 16.7 years) participating in a 22-week military-style "boot camp" program. Participants were mostly boys (73.1%), and most identified as White (55.7%) or Black (27.9%). As part of a larger study, participants completed the Alabama Parenting Questionnaire (APQ; Frick, 1991), and the Personality Assessment Inventory-Adolescent (PAI-A; Morey et al., 2007). Bi-variate correlations were conducted between subscales of the APQ (Positive Parenting (PP), Parental Involvement (PI), Inconsistent Discipline (ID), and Poor Monitoring/Supervision (PMS)) and the substance use subscales of the PAI-A (Drug Problems and Alcohol Problems). The Alcohol Problems subscale was positively associated with PMS ($r(150) = .311$, $p < .001$) and ID ($r(150) = .164$, $p < .05$). The Drug Problems subscale was also positively correlated with PMS ($r(152) = .318$, $p < .001$), and ID ($r(153) = .173$, $p < .05$) and negatively associated with PI ($r(153) = -.165$, $p < .05$) and PP ($r(153) = - .230$, $p < .004$). Results suggest that parenting practices are relevant for the initiation and escalation of drug and alcohol use in adolescents. This is consistent with previous literature indicating that negative parenting factors are associated with increased adolescent drug and alcohol use (Nichols et al., 2022) and could inform the development of parent-based interventions to prevent and reduce the impact of substance use disorders in adolescents by increasing positive parenting practices and reducing negative parenting practices.

Poster 66

Biomarkers of Neuroplasticity and Immune Function as Predictors of Behavioral Treatment Outcomes in Alcohol Use Disorder

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Alcohol-Associated Liver Disease (ALD) affects up to 51% of individuals with Alcohol Use Disorder (AUD) and can be fatal. Though brief interventions such as motivational interviewing (MI) are effective in reducing alcohol use, variability of treatment response requires further investigation. This study examined biomarkers of neuroplasticity and immune function as predictors of MI outcomes in individuals with AUD. We hypothesize that elevated inflammatory biomarkers (cytokines, chemokines, acute phase proteins) would predict attenuated response to MI and higher neuroplasticity (BDNF) would predict increased response to MI. In a 3-month NIH-funded clinical trial in adults (n=33; 48% women; mean age = 46) with moderate-to-severe AUD and with or at risk for ALD, participants underwent a baseline MI session and a 30-minute booster session at week 3. Drinking and cue induced craving were assessed at pre-intervention and 3-month follow-up. Plasma levels of BDNF, MCP-1, CD14, CD163, IL-6, IL-8, IL-18, LBP, and TNF-a were collected prior to intervention. Linear mixed models tested baseline biomarkers as predictors of change in alcohol use (average drinks/week, percent drinking days, and average drinks/drinking day) and cue-induced craving (single-item craving, Alcohol Craving Questionnaire total score), controlling for Alcohol Use Disorder Identification Test score. Higher IL-6 predicted greater drinks/week ($p=.004$), percent drinking days ($p=.006$), and drinks/drinking day ($p=.007$) at follow-up. Higher MCP-1 predicted greater percent drinking days ($p=.016$) at follow-up. No biomarkers were significant predictors of craving. Elevated inflammatory biomarkers warrant further investigation as prospective predictors of blunted treatment response to MI for AUD.

Poster 67

Prolonged onset and exacerbated symptoms: Withdrawal effects of Xylazine and Fentanyl co-exposure in adult male mice

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Understanding the mechanism(s) underlying behavioral effects induced by substances such as xylazine is of great importance as its use and abuse has emerged as a serious public health threat. Xylazine, also known as "tranq," is a non-opiate sedative, analgesic, and muscle relaxant. When used in combination with opioids, xylazine significantly enhances analgesic activity, respiratory depression, and vascular constriction, leading to increased mortality. When coupled with opioids, xylazine increases their sensitivity, prolonging their effects in humans and animals. Despite negative consequences of its use/abuse, the mechanism(s) underlying xylazine's actions are not well understood, and the behavioral effects it produces when combined with opioids are virtually unknown. Therefore, this study assessed withdrawal symptoms in adult male C57BL/6J mice following concomitant xylazine and fentanyl exposure. After acclimation, the mice received twice daily injections of xylazine (0.0 or 0.5 mg/kg) and Fentanyl (0.0 or 0.2 mg/kg) for seven days. On day 8, the opioid antagonist naloxone (1.0 mg/kg) was given to precipitate withdrawal, and symptoms were assessed at 0, 4, 8, 16, 24, 36, and 48 h. Our results indicate that xylazine lengthens the onset of withdrawal when compared to the fentanyl group. Fentanyl only treated groups showed significantly more withdrawal symptoms when compared to their respective controls, while co-exposure to xylazine, and higher doses of fentanyl, exacerbated withdrawal symptoms. These results suggest that xylazine delays the onset of withdrawal, while fentanyl alone or in combination with xylazine leads to significantly enhanced withdrawal symptoms.

Poster 68

Abstinence from methamphetamine decreases glutamate release from the orbitofrontal cortex to direct pathway spiny projection neurons in the dorsomedial striatum

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Methamphetamine (meth) is an addictive stimulant with rising rates of illicit use worldwide (Jones et al., Addict. Behav., '23). The dorsomedial striatum (DMS) (primarily composed of direct (dSPNs) and indirect pathway spiny projection neurons) is involved in regulating goal-directed behaviors (Balleine, et al., Curr. Opin. Behav. Sci., '21) and receives glutamatergic input from multiple cortical regions including the orbitofrontal cortex (OFC) which is also implicated in goal-directed actions (Schoenbaum et al., Nat Rev Neurosci., '09). Multiple studies show that drugs of abuse disrupt OFC-DMS communication which suggests dysfunction in neural circuits regulating goal-directed behaviors. (Cheng et al., Neuropharmacol., '21; Gremel et al., Nat Comm., '13) however, potential meth-induced OFCDMS circuit dysfunction is unclear. We hypothesized that abstinence from meth self-administration would disrupt OFC-DMS connectivity. To test this, transgenic male mice expressing D1-TdTomato and D2-GFP fluorescent probes were implanted with catheters and allowed to self-administer meth (2hrs/d; 0.1mg/kg/inf) for 10-days using fixed ratio 1 schedule of reinforcement; saline-yoked control subjects were run in parallel. After completing operant procedures, mice were bilaterally injected with pAAV-CamKII-chronos-BFP into the OFC; after 21-24 days of abstinence, ex vivo brain slices entailing the DMS were collected, and presynaptic release from OFC to DMS dSPNs assessed by measuring optogenetically stimulated paired pulse ratios using whole-cell patch clamp electrophysiological techniques. Glutamate release probability from OFC onto DMS dSPNs was decreased in mice that self-administered meth compared to saline-yoked control mice (meth: n=9 cells/3 mice, saline: n=9 cells/3 mice; unpaired t-test, $p=0.0392$). Results suggest impaired cortical input to DMS dSPNs that may contribute to a loss of cognitive control over striatal mediated goal-directed behavior.

Poster 69

Discriminative Stimulus Effects of Gabapentinoids: Investigating Voltage-Gated Calcium Channel and Mu Opioid Receptor Mechanisms in Male Rats

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Gabapentinoids (gabapentin and pregabalin) block the α2δ-subunit of voltage-gated calcium channels (α2δ-VGCCs) and are commonly used with opioids. The role of gabapentinoids in opioid misuse remains understudied. In rats discriminating fentanyl from saline, gabapentinoids and nimodipine, a blocker at the α1-subunit of VGCCs (α1-VGCCs), enhance the potency of mu opioid receptor (MOR) agonists to produce discriminative effects; moreover, (±)-BAY-K-8644, an α1-VGCC agonist, attenuates the ability of gabapentinoids and nimodipine to enhance the potency of MOR agonists to produce discriminative effects. Using 8 male rats discriminating 10 mg/kg gabapentin from saline (i.p.), this study assessed interactions between gabapentinoids and α1-VGCC ligands and between gabapentinoids and opioid receptor ligands to see whether α1-VGCC blockade and a MOR component contribute to an in vivo effect of gabapentinoids. Gabapentin (1.0-32 mg/kg), pregabalin (1.0-32 mg/kg), and nimodipine (0.0032-0.1 mg/kg), but not (±)-BAY-K-8644 (0.1-3.2 mg/kg), fentanyl (0.001- 0.032 mg/kg), heroin (0.01-0.32 mg/kg), buprenorphine (0.001-0.032 mg/kg), or carfentanil (0.0001-0.0032 mg/kg) elicited significant gabapentin-appropriate responding. The opioid receptor antagonist naloxone (1.0 mg/kg) did not significantly shift the gabapentin or pregabalin discrimination dose-effect functions, while (±)-BAY-K-8644 (0.01-0.1 mg/kg) shifted the discrimination dose-effect functions of both gabapentinoids significantly to the right. Carfentanil (0.032-0.32 mg/kg) shifted both gabapentinoid dose-effect functions significantly to the left. Results from this study suggest the discriminative effects of gabapentinoids arise from α1-VGCC blockade, without a MOR component. This study was supported by the USPHS grant R01DA058018 (TH) and the Welch Foundation grant AQ-0039 (CPF).

Poster 70

Effects of Cannabinoid (CB) 1 Receptor Neutral Antagonists on Fentanyl-Induced Conditioned Place Preference and Antinociception

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Accumulating evidence suggests that there are functional interactions between opioid and cannabinoid systems, making CB1 receptors a promising therapeutic target for opioid use disorder. Studies have reported that the CB1 inverse agonist rimonabant reduces drug-seeking behavior in animals, including heroin and morphine self-administration in rats and morphine-induced conditioned place preference in mice. However, rimonabant has significant safety concerns due to psychiatric side effects in human trials which may be due to its inverse agonist properties. CB1 neutral antagonists have been shown to have a more favorable side effect profile than rimonabant, and it has been hypothesized that neutral CB1 antagonists may also reduce the rewarding effects of opioids. The present studies were undertaken in male CD-1 mice to evaluate the ability of rimonabant and neutral CB1 antagonists AM6527 and AM4113 to modify the rewarding (conditioned place preference) and antinociceptive (warm water tail withdrawal assay) effects of fentanyl. Results show that both the inverse agonist rimonabant and neutral antagonists AM6527 and AM4113 produced dose-dependent reductions in the acquisition and expression of place preference induced by 0.32 mg/kg of fentanyl. These studies suggest that CB1 antagonists can reduce the rewarding effects of fentanyl. In the warm water tail withdrawal assay, the same doses of CB1 antagonists that blocked CPP did not produce antinociceptive effects alone and failed to substantively modify the antinociceptive effects of fentanyl. Taken together, this data provides further evidence that targeting the CB1 receptor with neutral CB1 antagonists may be a viable strategy for countering the abuse-related behavioral effects of fentanyl without interfering with its antinociceptive effects.

Poster 71

The impact of dietary manipulation and morphine on animal models of stress, aggression and defensive behavior

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Opioids are prescribed at high rates for patients with obesity, sometimes leading to tolerance with chronic use. Chronic morphine, as well as dietary manipulation (i.e. food restriction) have also been associated with impacts on mood/stress, though the potential interaction of these variables has not been evaluated in rodent models. The present study examined the impact of dietary manipulation on sensitivity of rats treated with chronic morphine to evaluate the hypothesis that food restriction and/or high fat diets would enhance stress, aggressive and defensive behaviors. 24 male Sprague-Dawley rats were fed either a standard laboratory chow (17% kcal from fat) a high fat/high carbohydrate chow (60% kcal from fat) or a ketogenic chow (90.5% kcal from fat). Rats either had free or restricted access to these diets. Rats were injected with saline or doses of morphine (3.2 – 56 mg/kg, increasing in quarter log doses every 3 days) twice a day over a 6-week period to induce tolerance and dependence. Aggressive and defensive behaviors were assessed at several points during the experiment using the Bottle-Brush Test (BBT) where rats were probed with a bottle brush, and behavioral scores were collapsed across multiple trials. To assess stress throughout the experiment, automated Rat Grimace Scale (RGS) was evaluated using video capture of behavioral cues (i.e., facial expressions) associated with pain and distress. Data from both assays were analyzed using ordinary one-way ANOVAs. Data collection is still in progress, but statistical trends reveal that RGS scores were decreased following acute morphine exposure, while aggressive behaviors during the BBT increased during chronic morphine exposure. Further, food restricted rats displayed more aggressive behaviors in the BBT than rats with free access. These results suggest that dietary considerations might impact mood symptoms associated with chronic morphine treatment.

Poster 72

Shifted balance between ventral striatal prodynorphin and proenkephalin biases development of cocaine place avoidance

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Evidence from human self-report and rodent models indicate acute cocaine can induce a negative affective state marked by panic and anxiety, which may reduce future cocaine use. However, there is limited information on how best to model this aversive state, and the mechanisms underlying acute cocaine aversion are unclear. In the striatum, dynorphin is associated with dysphoria following cocaine withdrawal, and enkephalin is associated with cocaine reward. We hypothesized that high striatal dynorphin and low striatal enkephalin would be associated with the acute cocaine's negative affective state and drive cocaine avoidance. To test this, we used a trace conditioning procedure, wherein cocaine is administered immediately after removal from the place conditioning apparatus. This approach conditions place avoidance (CPA) for several drugs of abuse by evidently pairing the drug's transient negative affective state with the preceding context. We found that wildtype mice (n=103) exhibit variable cocaine conditioning scores, which became more polarized over conditioning (RMANOVA), with approximately equal proportions developing preference and avoidance (X2). We next correlated CPA scores with striatal gene expression levels for enkephalin (Penk) and dynorphin (Pdyn) using qPCR (n=30). To our surprise, CPA was correlated with low Pdyn levels and a low Pdyn:Penk ratio in the ventral striatum. Consistent with this, mice with higher striatal Pdyn relative to Penk were more resistant to developing CPA than littermate controls (GLM, n=34). Our findings suggest striatal dynorphin has opposing roles in mediating the aversion associated with acute cocaine intoxication versus cocaine withdrawal.

Poster 73

Translating medication effects for alcohol use disorder across preclinical and clinical trial outcomes using meta-analysis

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Animal models are used for preliminary testing of novel compounds for alcohol use disorder (AUD). However, it is unclear whether early efficacy in preclinical models reliably predicts efficacy in clinical trials. We searched the literature for medications tested for AUD in preclinical models (i.e., two-bottle choice [2-BC] and operant reinstatement) and randomized clinical trials (RCTs). For preclinical models, we computed medication effects on 2-BC alcohol preference and consumption (k=77 studies, 14 medications) as well as operant reinstatement (k= 18 studies, 8 medications). For RCTs, we computed medication effects on RCT endpoints including return to any drinking and return to heavy drinking (k= 139 studies, 19 medications). We used medication as the unit of analysis and applied the Williamson-York bivariate weighted least squares estimation to preserve the errors in both the independent and dependent variables. Medication effects on 2-BC alcohol preference ($\beta\beta$=0.04, p= 0.004) and reinstatement ($\beta\beta$=0.20, p=0.05) were positively associated with medication effects on return to any drinking in human clinical trials but no associations were found on other RCT outcomes tested. Medication findings on 2-BC alcohol preference and operant reinstatement track medication effects on select clinical trial outcomes, specifically return to any drinking. This study provides empirical support for the association between medication effects across species and experimental models, a critical, yet untested, premise of preclinical studies in medications development.

Poster 74

Neural Correlates Underlying Sex and Strain Differences in Methamphetamine-Induced Conditioned Place Preference in Adolescent Mice

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There are sex differences in the use of methamphetamine (METH), with women initiating use earlier and transitioning to regular use faster than men. However, most rodent studies investigating the cellular basis of addiction use adult males. We employed a conditioned place preference (CPP) paradigm to investigate sex differences in the rewarding effects of METH in two strains of mice, C57Bl/6 and 129Sv/Ev. CPP began during adolescence (postnatal day 41), which is when substance abuse usually begins in humans. To evaluate the neural correlates of METH-induced CPP, mice were perfused 90 minutes after the CPP test (drug-free) and immunohistochemistry was used to label cells expressing the neural activity marker c-Fos. Behaviorally-induced upregulation of c-Fos in the nucleus accumbens (NAc) core, NAc shell and the CA1 subregion of the hippocampus was quantified using ImageJ software. Our results revealed a sex and strain difference in the behavioral and cellular effects of METH. In the C57Bl/6 strain, METH induced CPP in females only, effects that were associated with an increase in the number of c-Fos positive (+) cells in the NAc shell and the ventral pole of area CA1. In contrast, in the 129Sv/Ev strain, METH induced CPP in males only, which was also associated with more c-Fos+ cells in the NAc shell and ventral CA1. These results are suggestive of a NAc-CA1 circuit mediating the rewarding effects of METH during adolescence. Our findings may inform the selection of an appropriate background strain in future studies using transgenic mice to target underlying mechanisms.

Poster 75

The effect of fentanyl-associated cues on temperature and hyperalgesia in mice

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Fentanyl (FTN) is a potent synthetic opioid that is responsible for the rise in overdose deaths in the United States. During intoxication, opioids influence thermoregulation by causing hyperthermia, whereas in withdrawal, they have an opposite effect, i.e., hypothermia. Additionally, opioid intoxication causes analgesia, whereas hyperalgesia (i.e., enhanced pain) is observed in withdrawal. Cues that are paired with FTN can also become conditioned to effects of opioid intoxication and withdrawal. These cue-induced behavioral and physiological changes may drive opioid craving. We hypothesize that the exposure to FTN-associated cues would cause hyperthermia and reverse hyperalgesia during spontaneous withdrawal. Mice received daily subcutaneous injections of saline or escalating doses of FTN (0.12-1.00 mg/kg) to model opioid-naïve and opioid-dependent states. After that, mice received a single dose of the preferential μ-opioid receptor antagonist naloxone (NLX) to precipitate withdrawal. FTN and NLX treatments were each paired with different scent cues, and body temperature and mechanical sensitivity were measured in the presence of the cues. In dependent mice, low doses of FTN (0.12, 0.25 mg/kg) increased temperature, whereas high doses (0.50, 1.00 mg/kg) decreased temperature. At 0.50 mg/kg, we observed a biphasic change in temperature, with an initial decrease in the first 30 min following FTN, and a subsequent increase between 45 and 120 min after FTN. Administration of NLX after FTN-paired cue-conditioning reversed FTN-induced hypothermia. When we exposed the dependent mice to the cues only, both the FTN- and NLX-associated cues induced hyperthermia. Furthermore, FTN-associated cues alleviated opioid withdrawal-induced hyperalgesia in the dependent mice, but NLX-associated cues had no effect. These findings underscore the role of opioid-related cues in modulating body temperature and nociception during opioid dependence.

Poster 76

Potentiation of morphine-induced antinociception through Gβγ inhibition: evidence for a central mechanism

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Inhibition of Gβγ subunits with the small molecule, gallein, downstream of mu-opioid receptor (MOR) agonist-induced activation has been shown to potentiate morphine-induced antinociception without enhancing opioid-related side effects. However, it is unknown whether these effects of gallein are dependent upon activation of MOR and, if so, which MOR population(s). Therefore, the goal of the current study was to evaluate MOR-dependency of enhancements in morphine-induced antinociception by gallein and, subsequently, to assess which MOR populations are necessary for this effect. Antinociception was measured in female and male C57BL/6 mice using the warm water tail withdrawal (WWTW, 55°C) and hot plate (HP, 52°C) assays. Gallein pretreatments were administered either centrally at 30 min (100 nmol, i.c.v. or i.t.) or systemically at 24 hrs (100 mg/kg, i.p.) prior to morphine. Potentiation of morphine-induced antinociception was absent in MOR knockout mice pretreated with central gallein and in mice pretreated with systemic gallein and naloxone (3.2 mg/kg, i.p.) in WWTW. Furthermore, potentiation of morphine-induced antinociception was not blocked in mice pretreated with systemic gallein and naloxone methiodide (NLXM, 10 mg/kg, i.p.) in WWTW. However, centrally administered NLXM (10 nmol, i.c.v.) was able to block enhancements in morphine-induced antinociception by gallein in this assay. Together, these data suggest that gallein requires activation of central MORs to potentiate morphine-induced antinociception in the WWTW assay. Notably, gallein also enhanced morphine-induced antinociception in the HP assay (where nociceptive responses are thought to be supraspinally mediated). Yet, when administered intrathecally, gallein (100 nmol, i.t.) gallein does not have an effect in the WWTW. These data are consistent with our previous results demonstrating gallein-dependent enhancement of MOR-dependent inhibition of GABA release in the PAG (Sanchez 2022).

Poster 77

Characterizing Sleep Disturbances following Partial Sciatic Nerve Ligation in Sprague Dawley rats

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Sleep disturbances are a common symptom of chronic pain that are not adequately alleviated by currently available analgesics. Considering that sleep disturbances are associated with increased pain sensitivity and decreased quality of life, it is essential to develop treatments that improve sleep in chronic pain patients. In the present studies, we assess the effects of partial sciatic nerve ligation (PSNL; model of chronic pain) on the longevity and severity of sleep disturbances in relation to pain sensitivity in 11 male and 11 female Sprague Dawley rats implanted with wireless electroencephalography (EEG) transmitters. In PSNL animals, ⅓ of the sciatic nerve was ligated with silk suture; in the sham group the sciatic nerve was exposed but not ligated. EEG recordings, Von Frey, and acetone testing were taken throughout the study to assess sleep duration, sleep quality, and mechanical and cold sensitivity. EEG data were manually scored as wake, rapid eye movement (REM), and Non-REM sleep in 10-second epochs to assess sleep duration. During von Frey testing, filaments of different forces were applied to the palm of the hind paw to determine the 50% percent paw withdrawal threshold. In the acetone cold sensitivity test, acetone was applied to the paw and the duration of paw withdrawal or licking was measured. Data collection and analysis is ongoing at further timepoints and will be examined using within-subject and between subject analyses to correlate duration and severity of sleep disturbances with pain sensitivity. Together, these experiments will gain insight into how chronic pain affects sleep and will build the foundation for future studies to investigate novel analgesic/sleep-promoting therapies that minimize pain-induced sleep disturbances.

Poster 78

Methamphetamine-Induced Cognitive Impairment: From Neurovascular toxicity to Behavioral Deficits

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Methamphetamine (METH) abuse is strongly linked to severe cognitive dysfunction, yet the mechanisms driving neurotoxicity and behavioral impairments remain poorly understood. This study explores the impact of chronic METH exposure on neurovascular integrity, neuroinflammation, and synaptic function, correlating these changes with cognitive deficits. Using preclinical models, we assessed learning, memory, and executive function through behavioral assays, revealing that METH administration induces significant neuroinflammation, marked by heightened microglial activation and elevated pro-inflammatory cytokines in the hippocampus and prefrontal cortex. Additionally, METH exposure disrupted neurovascular function, leading to blood-brain barrier (BBB) dysfunction, increased permeability, and reduced expression of tight junction proteins, thereby compromising neurovascular health. These pathological changes closely correlated with deficits in spatial learning and memory, as demonstrated in the Y-maze and novel object recognition tests. Furthermore, chronic METH exposure triggered endoplasmic reticulum (ER) stress and autophagy dysfunction, contributing to neuronal damage and exacerbating cognitive decline. Our findings establish a mechanistic link between METH-induced neurotoxicity and cognitive impairment, emphasizing the critical roles of neurovascular dysfunction and neuroinflammation. Understanding these pathways may facilitate the development of targeted therapeutic strategies to mitigate METH-related cognitive deficits.

Poster 79

Effects of Altering μ-Opioid Receptor Functioning Within the Nucleus Accumbens Shell in Differentially Reared Male and Female Rats

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It is well established that differential rearing alters both the hedonic responding and incentive motivation for rewards. Specifically, when compared to social housed rats, socially isolated rats display fewer hedonic reactions for non-drug rewards while displaying increased incentive motivation for non-drug rewards. One component that is implicated in modulating the hedonic value of a reward is the mu(μ)-opioid receptor (MOR), specifically located within the nucleus accumbens shell (NAcS); a region that plays an essential role in hedonic responding and incentive motivation. Previous studies suggest that administering a MOR agonist into the NAcS increases the hedonic value of sucrose. However, there is a gap in pre-existing literature examining the effects of MOR functioning in differentially reared rats. In the present study we aimed to address this gap to determine if MOR functioning within the NAcS contributes to reduced hedonic responding in socially isolated rats. Male and female Long-Evans rats (n = 27) were reared in one of three different rearing environments, isolated (IC;n = 7), standard (SC;n = 12) and enriched (EC;n = 8). Prior to taste reactivity sessions, rats were microinjected with 3 different concentrations of the MOR agonist, DAMGO; control (saline), low (0.01ug), high (0.1ug) in the NAcS to measure its effect on the hedonic value of two different sucrose concentrations (low (0.1M), high (0.5M)). Repeated measures ANOVA and Tukey's post-hoc analyses revealed that DAMGO microinjections increase hedonic responding to sucrose in EC and SC rats but not IC rats, regardless of sex. These results suggest that social isolation alters MOR functioning within the NAcS in both male and female rats and this altered MOR functioning may contribute to the increased incentive motivation for non-drug rewards in socially isolated rats.

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Unraveling the Role of Interpeduncular Nucleus Glucagon-like Peptide-1 Receptor Agonism in Fentanyl-Induced Striatal Dopamine Signaling

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In the United States, fatal opioid overdose continues to be one of the leading causes of preventable death. Thus, it is critical to understand the central mechanisms underlying fentanyl seeking to further the development of novel effective treatments for fentanyl use disorder (FUD). Our lab has shown that glucagon-like peptide-1 receptor (GLP-1R) activation in the interpeduncular nucleus (IPN) reduces fentanyl-seeking behavior in rats. Additionally, we found that GLP-1Rs and mu opioid receptors are co-expressed on IPN inhibitory neurons that project to the laterodorsal tegmental nucleus. These neurons preferentially send excitatory signals to ventral tegmental area dopaminergic neurons that then project to the nucleus accumbens (NAc). Given these findings and that NAc dopamine signaling is important for opioid-primed reinstatement, we hypothesized that IPN GLP-1R activation will reduce NAc dopamine signaling in response to an acute injection of fentanyl. We recorded dopamine signaling using fiber photometry in male and female rats, comparing fentanyl-naive and fentanyl-dependent groups. We injected GLP-1R agonist Exendin-4 (Ex-4) (0 or 0.1 μg) into the IPN immediately before fiber photometry recordings. After ten minutes of recording, we administered an acute infusion of fentanyl (0 or 12.5 μg/kg, i.v.). We showed that 12.5 μg/kg fentanyl (i.v.) increased dopamine sensor fluorescence in the NAc. We are currently analyzing the effect of intra-IPN Ex-4 and previous fentanyl experience on fentanyl-induced dopamine release. This study explores the complex role of the IPN and IPN GLP-1Rs in fentanyl-mediated dopamine signaling and may provide further support for using GLP-1R agonists as a treatment for FUD

Poster 81

Phytocannabinoids modulate adipose tissue fatty acid oxidation and adipocyte browning during HIV/SIV infection under ART

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Antiretroviral therapy (ART) has greatly extended the life expectancy of people living with HIV (PLWH). However, non-AIDS-related conditions such as cardiovascular disease (CVD), liver failure, and type 2 diabetes (T2D) remain widespread, with dyslipidemia, driven by both HIV and ART playing a key role. New therapies are needed to comprehensively target both inflammation and dyslipidemia. Mesenteric adipose thickness is strongly linked to metabolic syndrome and coronary artery disease. Given that long-term Δ9-tetrahydrocannabinol (Δ9-THC) reduces intestinal inflammation in SIV-infected rhesus macaques (RMs), we hypothesized that a THC:CBD combination with ART may have therapeutic effects on mesenteric adipose tissue. To investigate this, we performed bulk RNA sequencing on whole mesenteric adipose tissue from ART-treated SIV-infected RMs that received either a vehicle control (VEH/SIV/ART; n=8) or THC:CBD (1:3) (THC:CBD/SIV/ART; n=4), as well as pre-infection samples (n=11). THC:CBD supplementation significantly increased the expression of PPARA and CPT1A at both the mRNA and protein levels, suggesting enhanced free fatty acid oxidation in mesenteric adipose tissue under SIV/ART. Additionally, UCP2, a gene associated with reduced obesity, decreased adipose inflammation, and increased adiponectin production was significantly upregulated in the THC:CBD group at both the mRNA and protein levels. Moreover, UCP1 protein levels were notably elevated in the THC:CBD group, accompanied by a shift in adipocyte morphology from white to brown-like, indicating increased thermogenesis and fatty acid oxidation. This suggests a reduction in adiposity and obesity under SIV/ART. Ingenuity Pathway Analysis predicted reduced inflammation, increased adipocyte browning and enhanced fatty acid oxidation pathways in the THC:CBD/SIV/ART group. Overall, these findings suggest that cannabinoids may have broader therapeutic applications beyond PLWH, particularly in promoting cardiovascular and metabolic health.

Poster 82

Assessing Withdrawal Signs Resulting from Fentanyl+Xylazine Co-Use

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The ongoing U.S. opioid epidemic caused 108,000 deaths in 2023, with rising concerns over xylazine (XYL), an α2 adrenergic agonist and animal sedative, in the drug supply. The U.S. Office of National Drug Control Policy emphasized the urgent need for research on fentanyl (FENT) + XYL interactions, overdose, and withdrawal. XYL has been reported to enhance fentanyl's effects and delay withdrawal, which may contribute to co-use, complicate treatment efforts, and potentially increase relapse risk. The goal of this study is to directly compare the withdrawal syndrome that emerges after extended (12-hr) access to FENT (3.2 µg/kg/inf) alone, or in combination with XYL (3.2-100 µg/kg/inf). Male and female Sprague-Dawley rats were implanted with a venous catheter and allowed to acquire responding for FENT alone. Once the rats were stable on FENT, we introduced varying mixtures of FENT+XYL, which were available 12-hrs per day for 5 consecutive days. Somatic withdrawal signs and sensitivity to mechanical nociception were assessed 8, 24, 48, and 60 hrs after the 5th 12-hr session of the week. The addition of low-dose XYL (3.2–10 µg/kg/inf) did not alter total drug intake, whereas higher doses (32–100 µg/kg/inf) led to a significant reduction. Withdrawal severity increased with XYL co-administration, with the 3.2 and 10 µg/kg/inf doses producing higher somatic withdrawal scores compared to FENT alone. Unusual withdrawal signs, including sneezing, quick movements, and jumping, emerged specifically with FENT+XYL mixtures. Paw withdrawal thresholds remained comparable across all doses of XYL. This preliminary data suggests that XYL can enhance the withdrawal severity. However, additional work is needed to determine how withdrawal from FENT+XYL impacts the abuse related and toxic effects of FENT+XYL co-use.

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Behavior and Perineuronal Net Expression Following Repeated Co-Administration of Nicotine and Oxycodone

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Nicotine and opioids are often components of polysubstance drug combinations. Recent findings in our lab have confirmed that repeated drug administration may alter perineuronal net (PNN) expression in the frontal cortex. The goal of this project was to examine how repeated administration of nicotine and opioids influences nociception (processing of noxious stimuli), behavioral tolerance and neuroplasticity-related proteins. Male and female Wistar rats were treated with saline, nicotine (0.4-3 mg/kg i.p.), oxycodone (2 mg/kg s.c), or a combination twice daily for seven days. Thermal nociception was measured using a tail withdrawal test and thermoregulation was measured using rectal temperature assessments. Whole brain coronal slices were collected to identify Wisteria Floribunda Agglutinin (WFA)-positive PNNs and parvalbumin (PV) expressing neurons within 24 hours of the last drug session. Results confirmed that males and females expressed significant antinociceptive and thermoregulatory effects following acute administration of nicotine and oxycodone combination, as well tolerance following repeated administration ($p<0.05$). Preliminary immunohistochemical data confirmed an increase in PNN density (count/mm2) and a decrease in PNN intensity (arbitrary units) when compared with controls. These data confirm that opioid, nicotine, administration in rats may alter perineuronal net expression important to memory and reward with changes in behavior.

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Poster 84

Interrogation of Striatal Opioid Peptides on Cocaine Approach-Avoidance in Mice

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Cocaine evokes a strong positive affective state, making it a powerful reinforcer with high addictive potential. However, evidence from human self-report and rodent models indicate cocaine can also induce a negative affective state marked by panic and anxiety. While this may reduce future cocaine use, it can also lead to worse addiction outcomes, such as co-use with opiates. Despite this, the understanding of the mechanisms driving cocaine avoidance are limited. Within the striatum, heightened tone of the opioid peptide enkephalin or activation of µ-opioid receptors facilitates cocaine reward, while high levels of dynorphin are aversive. We therefore hypothesized that low striatal enkephalin and/or high dynorphin would be aversive and increase avoidance to self-administer cocaine. To test this, we measured the development of an approach-avoidance conflict to self-administer cocaine using a runway apparatus. We predicted the inbred mouse strains, C57Bl/6J (n=24) and DBA/2J (n=38), would show divergent avoidance behaviors because they have opposing striatal levels of enkephalin and dynorphin. We found that both strains exhibit cocaine avoidance, though they express it differently. Compared to food self-administration controls, 2W-RMANOVA showed DBA/2J mice increased their latency to self-administer cocaine over training, while C57Bl/6J increased the number of retreats from the cocaine goal box. To determine if pre-existing low levels of striatal enkephalin increases cocaine avoidance, we tested mice with a selective deletion of enkephalin from striatal neurons (D2-PenkKO, n=34). Compared to littermate controls, D2PenkKOs showed a similar increase in the latency to self-administer cocaine across trials, indicating that low striatal enkephalin is not sufficient to induce cocaine avoidance in this task. Taken with previous literature, heightened striatal enkephalin augments cocaine's positive affective state, but low striatal enkephalin does not mediate its negative affective state.

Poster 85

Self- Administration, Extinction, Progressive Ratio, and Histamine-Infused Cocaine: Its Effects on the Salience Network and Neuronal Activity

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Substance Use Disorder (SUD) is a common mental health disorder with chronic physiological effects. Despite the known short and long-term negative consequences associated with drug intake, many are vulnerable to addiction, and may maintain or increase their drug intake to achieve allostasis. Cocaine (C) manipulates the neural pathways responsible for reward and decision making, including insula-prelimbic projections (the 'Salience Network'). This study was conducted to determine the changes in neural firing involved with extinction, progressive ratio (PR), and self-administered (SA) cocaine if infused with histamine (H), and whether sex differences would impact their neural activity. We hypothesized that the negative aspects of these tasks (effort, punishment, absence of drug) would increase the excitability of the neuronal firing in comparison to SA alone. 8 Long Evans rats (n=2f, 6m) have undergone SA, PR, and extinction, recorded in operant chambers via nose poke. The salience network was examined by a miniscope camera, capturing neuronal images from a GRIN lens implanted in the anterior insular cortex. The data was processed by CalmAn and NeuroExplorer. Each rat underwent an infusion of viral Credependent GCaMP6s in the anterior insula, and a retrograde adeno-associated virus encoding Crerecombinase in the medial prefrontal cortex. Preliminary results show that in the extinction and PR trials, the control rats (water-saline (W/S)), had more non phasic neurons, while the cocaine rats had more excitatory and inhibitory signals. For the self-administrated (W/S and C) and histamine (infused with W/S and C) trials, the opposite was true. This demonstrated that the extinction and histamine trials showing the greatest difference in neuronal firing. The continued collection of data may prove to be useful in decelerating drug abuse to those seeking rehabilitation.

Poster 86

Preliminary characterization of the behavioral and physiological effects of e-cigarette withdrawal

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There is currently insufficient evidence on how e-cigarette withdrawal may differ from combustible cigarette withdrawal given differences in e-cigarette use topography and product constituents. The purpose of the current ongoing study is to evaluate the timecourse and clinical significance of e-cigarette withdrawal in a controlled residential laboratory setting. This preliminary analysis evaluates early evidence of withdrawal timecourse and association with post-discharge relapse. Participants (n=10; 7 male, 2 female, 1 non-binary) completed a 7-day residential research unit stay and underwent observed e-cigarette abstinence. Four-time daily measures were collected to assess subjective mood (e.g., craving), cognitive performance (e.g., sustained attention), and cardiovascular outcomes. Return to e-cigarette use was recorded at a one-week follow-up. Preliminary data were analyzed using linear mixed effect models evaluating the effect of day and interactions based on e-cigarette use status at followup. A significant effect of day was observed for heart rate ($p=.002$), attentional performance ($p<.001$), craving ($p<.001$), and subjective withdrawal ($p<.001$). Peak increases differed by endpoint with peak craving and subjective withdrawal observed on Day 2, peak disruptions in attention observed on Day 6, and peak heart rate elevations observed through discharge. Craving ($p<.001$) and subjective withdrawal ($p<.001$) differed by e-cigarette use at follow-up with participants reporting daily use at follow-up showing persistently elevated craving and withdrawal through the residential stay. These findings indicate variations in the timecourse of withdrawal symptoms with cognitive and physiological effects persisting compared to more immediate effects on craving and subjective withdrawal symptoms. Like cigarette withdrawal, the present findings suggest that the severity and persistence of withdrawal during e-cigarette abstinence may be a strong predictor of relapse.

Poster 87

Evaluating the Stimulant Effects of UR-1-1-8; A Novel Atypical Dopamine Transporter Inhibitor

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In previous studies, UR-1-1-8, a highly selective dopamine transporter inhibitor was demonstrated to have anti-inflammatory properties and reduce pain and motor impairments in a preclinical multiple sclerosis model. Here, we investigate the stimulant-like effects of UR-1-1-8 using the drug discrimination model. Eight Sprague Dawley rats (four males and four females) were trained to discriminate 0.32 mg/kg methamphetamine from saline. Methamphetamine dose-dependently increased drug lever responding, with an ED50 value of 0.146 (0.117—0.175) mg/kg. The ED50 value of cocaine for sharing effects with methamphetamine was 2.41 (0.412–3.87) mg/kg, which was 16.5 times less potent than methamphetamine. UR-1-1-8 was tested in doses that decreased response rates to 48.1 % percent of vehicle responses, but it did not substitute for methamphetamine (as measured by the maximum percentage of methamphetamine-lever responding of 25%). UR-1-1-8 (3.2 or 10 mg/kg) did not significantly modify the slope or the intercept of the of the dose-effect functions of methamphetamine or cocaine. In conclusion, UR 1-1-8 did not substitute nor alter the discriminative stimulus effects of methamphetamine, indicating that UR-1-1-8 does not share effects with this drug of abuse.

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Poster 88

Spatially resolved neuroimmune transcriptomic responses to TLR7 activation in mouse

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Neuroimmune activation in the brain is linked to excessive alcohol intake. TLR7, a pattern recognition receptor of the innate immune system, expression is upregulated in the brains of individuals with Alcohol Use Disorder (AUD). Repeated administration of the TLR7 agonist R848 induces an escalation of voluntary alcohol consumption (PMID: 32726684). Single- nucleus transcriptomic (snRNA-seq) profiling of micro-punches from the medial prefrontal cortex and amygdala of R848 treated animals shows transcriptomic changes in multiple cell types that are not restricted to immune cells; however, snRNA-seq does not retain the spatial information of the profiled cells and their interaction with neighboring cell types and is limited to a regional punch. We performed Xenium profiling on coronal brain sections from saline- and chronically treated R848 mice, generating spatially resolved subcellular transcriptome of ~800 K cells across the brain. We identified an R848-specific oligodendrocytes subcluster in the corpus callosum and fimbria of the hippocampus in proximity to the lateral ventricle. This cluster is enriched in C4b, a crucial component of the immune response complement system, and Serpina3. Both genes are immune markers previously shown to be enriched in disease-associated oligodendrocytes. This subcluster was additionally enriched in inflammation-related gene Cd9, interferon gene Ifi27, and interleukin gene Il33. The enriched genes were colocalized with canonical myelinating oligodendrocyte markers. Visium HD Spatial transcriptomic profiling of other samples showed increased C4b and myelinating oligodendrocyte markers co-localization in R848 treatment compared to saline, confirming the Xenium findings. This indicates that a subset of myelinating oligodendrocytes localized in proximity to the lateral ventricles acquires an immune-related role in response to TLR7 activation. Differential expression analysis showed lateral ventricles (LVs) ependymal cells to be highly susceptible to R848, showing dysregulation in the inflammatory response and cell junction genes. LVs produce cerebrospinal fluid that mediates communication between various brain regions; our analysis links chronic TLR7 activation to persistent spatial cell-type specific changes around the LVs, providing novel neuroimmune activation mechanisms that can be investigated for their potential roles in mediating escalation of alcohol drinking.

Poster 89

Therapeutic Potential of Terpenes and Cannabinoids: Modulating Inflammation and Pain in Preclinical Models

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The effects of terpenes and cannabinoids on inflammation and immune response are crucial in regulating immune system activity and maintaining immune balance. BCP, a terpene and CB2 receptor agonist, exhibits anti-inflammatory and neuroprotective properties, aiding in pain relief. Although CBD does not directly act as a CB2 receptor agonist, it modulates CB2 receptors to exert anti-inflammatory and neuroprotective effects. In vitro, both BCP and CBD reduced pro-inflammatory cytokine expression and reactive oxygen species (ROS) levels in RAW macrophages. Further, we assessed their therapeutic potential in pain management in Swiss Webster mice. BCP and CBD administered intraperitoneally alongside oxycodone, enhanced analgesia by up to twofold, depending on their concentrations. In Alzheimer's disease models (STZ toxin-induced and APP Knock-in), treatment with BCP reduced neuroinflammation, indicating its potential for addressing neuroinflammation in Alzheimer's and conditions like methamphetamine addiction.

Poster 90

Patterns of Ultrasonic Vocalizations in Rats Exposed to Chronic Ethanol Vapor

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Rats emit ultrasonic vocalizations (USVs) that reflect their emotional states, with 50 kHz USVs typically indicating positive states and 20 kHz USVs signaling negative states, including during withdrawal from substances of abuse like alcohol. While alcohol withdrawal is linked to increased 20 kHz USVs, the effects of chronic ethanol vapor exposure on USVs remain underexplored. This study examined the impact of ethanol vapor versus air exposure on 20 kHz and 50 kHz USVs in male and female Long-Evans rats. Baseline USVs were first recorded prior to any vapor exposure. After 10 days of intermittent ethanol vapor exposure (14 hr/day), USVs were recorded again 7-8 hours post-exposure during withdrawal. Recordings took place under undisturbed conditions and following the limb flexion test (a withdrawal marker). USVs were classified by affective bandwidth (20-29 kHz for negative; >30 kHz for positive) and frequency modulation (FM) patterns. Results showed an overall difference in call classifications during baseline ($p = 0.004$) and post-vapor ($p=0.006$) in males and females, which is mainly due to the greater number of FM 50kHz calls compared to other types of calls. No significant changes in USV calls were observed between pre (baseline) vs post vapor in any groups. However, during withdrawal testing, there was an overall difference in call classifications ($p < 0.001$) and number of USV calls pre vs post limb flexion test ($p < 0.05$). Both males and females displayed greater number of FM 50 kHz calls, particularly after the limb flexion test. Results suggest that USV calls linked to positive affect may increase during withdrawal from chronic ethanol vapor. Expanding the sample size will clarify vapor exposure's impact on emotional states.

Poster 91

Investigating the Insula to Medial Prefrontal Pathway in Distress Tolerance, Cocaine Self-Administration, Impulsivity, and Anxiety-Like Behavior

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Distress tolerance (DT) is the ability to persist in challenging, goal-directed activities while experiencing psychological stress. Low DT (or an inability to persist) and high impulsivity have been associated with heightened drug-seeking and relapse. Furthermore, anxiety can be considered a symptom of distress intolerance and is associated with heightened drug use. The insular (INS) and medial prefrontal cortex (mPFC) are brain regions linked to drug-seeking. Connectivity between these regions forms key cortical nodes of the Salience Network (SN), a network proposed to process the most relevant stimuli (i.e., drug craving) and coordinate a behavioral response. However, no preclinical studies have examined SN activity in DT and linked it to drug-seeking, impulsivity, and anxiety. We hypothesize that SN activity during the DT task will correlate with these behaviors, and that a history of cocaine use will disrupt this connectivity. To investigate this, viral infusions of Cre-dependent GCaMP6s in the INS and retrograde adeno-associated virus encoding Cre recombinase in the mPFC were performed. In the INS, a GRIN lens was implanted to monitor neural activity in freely behaving female (n=4) and male (n=8) Long Evans rats during a DT task. Subjects then underwent elevated plus maze (EPM) testing and cocaine or water self-administration (SA). Animals then began an abstinence period, after which DT, EPM, and neural activity were reassessed. We used chi-square analyses to assess differences in neural activity and experimental groups. Overall, our data suggest that the SN tracks events in the DT task and experiences changes in neuronal profiles after cocaine SA when compared to controls. Additionally, we observed sex-dependent changes in DT after SA. Our future work will expand upon these findings by further assessing these behaviors and INS-mPFC (SN) connectivity in DT.

Poster 92

Characterization of the discriminative stimulus effects of GLP-1 receptor agonist liraglutide in rats

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Glucagon-like-peptide-1 (GLP-1) receptor agonists have gained popularity as treatments for managing obesity and type 2 diabetes due to their ability to enhance blood sugar control, promote weight loss, and increase satiety. However, it is unclear if GLP-1 receptor agonists can serve as discriminative stimuli or be evaluated using the drug discrimination procedure. In order to establish liraglutide as a discriminative stimulus, 10 male Sprague–Dawley (n=10) rats were trained to discriminate an i.p. injection of liraglutide from saline while responding under a fixed-ratio 5 schedule for a food reinforcer. Following pilot testing to explore time course duration, a pretreatment time of 4 hours was used. To meet training criteria, 90% of total responses must occur on the correct lever, with fewer than 5 responses on the incorrect lever prior to the first reinforcer delivery, for 5 consecutive or 6 or 7 training sessions. After 34 days of using a smaller training dose (0.032 mg/kg) rats were moved to a final training dose of 0.056 mg/kg. After an average of 8 days, 4 of 10 rats met criteria to begin testing, with several additional rats close to meeting criteria, although these experiments are ongoing. Planned next steps include generating liraglutide dose-response curves as well as substitution tests using other GLP-1 receptor agonists (e.g., semaglutide, dulaglutide, exenatide), and combination tests using liraglutide, semaglutide, dulaglutide, or exenatide with selective antagonists for GLP and GIP receptors (e.g., exendin, ANTIGIP, GLP-1R). Additionally, substitution tests will be explored using drugs that also reduce feeding, via different pharmacological mechanisms of action (e.g., lorcaserin, cocaine, methamphetamine). The results of this study will further elucidate the in vivo pharmacological effects of liraglutide, and can guide future experiments with GLP-1 receptor agonists and antagonists as they gain popularity for additional health conditions, beyond metabolic disease.

Poster 93

Modeling polysubstance use: Rodent concurrent access to fentanyl and methamphetamine alone and in combination

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Since 2019, deaths attributed to the co-use of opioids (e.g. fentanyl) and stimulants (e.g. methamphetamine) has increased exponentially. Polysubstance users report co-use of opioid and stimulants to achieve a greater "high" and to attenuate symptoms of opioid withdrawal. Preclinical behavioral studies on opioid and stimulant mixtures are varied, with some studies indicating a synergistic effect and others indicating an additive to sub-additive effect. However, no studies have examined whether subjects prefer to use mixtures of fentanyl and methamphetamine over either drug alone. Utilizing a previously established concurrent access (two drug) self-administration procedure, male and female Sprague-Dawley rats were allowed to respond to earn infusions of fentanyl (0.0032 mg/kg/inf) or methamphetamine (0.1 mg/kg/inf) in the same session. The dose of the preferred (variable) was then manipulated to establish a dose-response curve for choice of the non-preferred (fixed). Subsequently, a small dose of the variable drug was added to the fixed-dose drug and the dose-response curve was re-established for the variable drug and mixture. Consistent with previous findings, four distinct phenotypes of responding were observed: (1&2) consistent responding for one drug over the other across sessions (strong preference), (3) exclusive responding for one drug in one session and the alternate drug in other sessions (indifference), and (4) within session responding for both drugs (co-use). Preliminary mixture data suggests preference for mixtures may be dependent on these observed phenotypes of responding. With research on polysubstance use lacking, this complex model has potential to help fill other knowledge gaps through the implementation of the many other factors that influence drug taking.

Poster 94

Discriminative stimulus effects of fentanyl and xylazine

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Xylazine-adulterated fentanyl (i.e., "tranq-dope") has been identified as a national public health threat in the United States. Despite the increasing prevalence of this drug combination, little is known about the interactions between fentanyl and xylazine on measures directly relevant to their abuse liability. The primary objective of this study was to determine whether xylazine enhances or prolongs the mu-opioid mediated discriminative stimulus effects of fentanyl. To this end, male and female Long-Evans rats were trained to discriminate the prototypical mu opioid agonist, morphine, from saline, and substitution tests were conducted with fentanyl, xylazine, and fentanyl-xylazine combinations. Fentanyl substituted fully for the morphine training stimulus, whereas xylazine failed to substitute for the morphine stimulus up to doses that significantly decreased response rates. In drug combination tests, xylazine disrupted stimulus control exerted by fentanyl, increasing drug-appropriate responding at low doses, decreasing drug-appropriate responding at high doses, and flattening fentanyl's dose-effect curve. The discriminative stimulus effects of a high dose of fentanyl decreased over the course of two hours. Xylazine disrupted the time course of fentanyl's discriminative stimulus effects, increasing drug-appropriate responding at longer intervals and decreasing drug-appropriate responding at shorter intervals. These data indicate that xylazine does not produce discriminative stimulus effects similar to prototypical mu opioid agonists and disrupts the mu-mediated discriminative stimulus effects of fentanyl. These findings further suggest that the co-use of xylazine and fentanyl is not due to a simple enhancement or prolongation of fentanyl's mu-mediated subjective effects.

Poster 95

Estrogenic contributions to female risk aversion

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Decision making is a cognitive process in which individuals assess options varying in their expected rewards and associated costs. There are robust sex differences in decision making, with females exhibiting greater risk aversion than males. Prior work shows that the ovarian hormone estradiol is a critical mediator of phenotypical female risk aversion; however, the specific mechanism by which estradiol exerts its effect on decision making is unknown. Further, the contribution of progesterone is yet unexplored in the context of risky decision making. To address these gaps in knowledge, female Long-Evans rats (n=18) were trained in the Risky Decision-making Task (RDT) in which rats choose between a small, safe food reward and a large food reward that is accompanied by a variable probability of footshock punishment. After achieving stable behavioral performance, rats were ovariectomized (OVX) and re-tested in the RDT. Rats then received an estrogen receptor α (ERα) agonist (PPT) or an ERβ agonist (DPN) via subcutaneous injection. These drugs were administered daily following RDT testing using a randomized within-subject design (PPT, 1mg/kg; DPN, 1mg/kg; PPT+DPN; vehicle, sesame oil) for 7 days with a minimum of 8 days between treatments. During each treatment and the successive washout period, estrous cycles were monitored. In a separate cohort of animals, the effect of progesterone (P4) on RDT performance was assessed using an identical within-subject design (P4, 0.6mg/0.1mL + 5% EtOH; vehicle, sesame oil + 5% EtOH). Administration of the ERα selective agonist PPT attenuated OVX-induced increases in risk taking, while administration of P4 did not affect risk taking. These data expand our understanding of hormonal regulation of female risk aversion and indicate that estradiol modulates female risk aversion via ERα activation.

Poster 96

Estradiol effects and sex differences in morphine withdrawal-induced anxiety-like behavior and the role of the NMDA receptor

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Sex differences and the influence of the female sex hormone estradiol on opioid withdrawal-induced anxiety remain understudied. We hypothesize that morphine withdrawal will increase anxiety-like behavior, that females will be less anxious than males, and that estradiol is anxiogenic during morphine withdrawal. Male and female Long-Evans rats were subjected to a chronic escalating dose of morphine over ten days. Lavage was performed to investigate the estrous stage of female rats. Morphine withdrawal-induced anxiety was assessed using the Elevated Plus Maze (EPM) 24 hours after the last dose of morphine. Rats underwent a 5 minute trial in the EPM. Female rats overall displayed less anxiety-like behavior with significantly greater time spent in open arms compared to male rats. Additionally, females with high estradiol levels (proestrus/estrus stage) on test day displayed increased morphine withdrawal-induced anxiety-like behavior in the EPM. Sex differences in morphine withdrawal-induced behaviors appear to correspond to variations in estradiol levels. We also investigated NMDA receptor involvement in these anxiety-like behaviors through Western blot analysis, focusing on the amygdala and ventral hippocampus, which are linked to anxiety. Preliminary data demonstrate a significant decrease in GluN2A-containing neurons in the ventral hippocampus in female morphine withdrawn rats. There is a significant increase in GluN2B-containing neurons in the basolateral amygdala in morphine-withdrawn female rats. There was an increase in GluN2B-containing neurons in the central amygdala (CeA) in male morphine-withdrawn rats. Also in the CeA, female morphine-withdrawn rats had fewer GluN2B-containing neurons than male morphine-withdrawn rats. Overall, NMDA receptor subunits differ in expression 24 hours after morphine withdrawal and across sexes in brain areas associated with anxiety-like behavior.

Poster 97

Context-Dependent Conditioning of Peripheral Nicotine Effects as Cues for Centrally mediated Locomotor Activity

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Purpose: Nicotine addiction is a major public health concern in the U.S. Despite available pharmacological and behavioral treatments, the success rate for smoking cessation in the U.S. is less than 10%. The role of the peripheral nervous system in the pathophysiology of nicotine addiction is not well understood. The purpose of this study was to evaluate the effect of peripheral nicotine receptor stimulation on locomotor activity in nicotine tartrate (NicT)-conditioned mice. Methods: To test whether nicotine's peripheral effects can cue a central response, we conducted a locomotor activity (LMA) conditioning study in Swiss-Webster mice. In the context-dependent study, three groups (n=8) received daily injections of saline, nicotine tartrate (NicT, 0.4 mg/kg), or peripherally restricted nicotine monomethiodide (NicM, 0.4 mg/kg) for five days, with LMA recorded. On Day 6, all groups received NicM. A context-independent study followed the same design, but injections occurred in home cages, and half of the NicT-exposed group received saline on Day 6. Results: In the context-dependent study, NicM on Day 6 mimicked NicT's initial locomotor depressant effect within the first 10 min in the NicT-exposed group. It did not produce any significant effect in the saline and NicM groups. This effect was absent in the context-independent study. Conclusion: Following context-dependent conditioning, the peripheral effects of nicotine can independently produce depressant effects that resemble the central effects of nicotine on locomotor activity. This result aligns with the hypothesis that the peripheral actions of nicotine can cue a central response. Future studies would explore conducting a saline challenge test after context-dependent conditioning. Exploration of different doses of NicT and NicM could also further elucidate the peripheral vs central contributions to nicotine reward.

Poster 98

Characterizing naloxone reversal of the cardiorespiratory depressant effects of opioids alone and mixtures of opioids and stimulants in rats

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Of the almost 74,000 fatal synthetic opioid overdoses in the United States in 2022, over half involved a stimulant (e.g., methamphetamine [METH]). Although there are effective treatments for reversing opioid-induced cardiorespiratory depression (OIRD) (e.g., NarCan®; naloxone), clinical evidence suggests that more frequent and/or larger doses are required to reverse overdoses involving opioids and stimulants. Because fentanyl has unique properties (e.g., muscle rigidity, vocal cord closure), we hypothesized that naloxone would be less potent and effective at reversing OIRD from fentanyl than heroin, and for a fentanyl + METH mixture than fentanyl alone. Using pulse oximetry in male and female Sprague-Dawley rats (n=48/sex), this study characterized the effects of intravenous (IV) fentanyl (0.0056-0.56 mg/kg), heroin (0.32- 5.6 mg/kg), METH (0.1-1 mg/kg), or mixtures of 0.56 mg/kg fentanyl + 1 mg/kg METH or 5.6 mg/kg heroin + 1 mg/kg METH on blood oxygen saturation (SpO2), heart rate (HR), and breath rate (BR). Naloxone (0.01-3.2 mg/kg; IV) or vehicle was administered 5 minutes after to assess reversal. Naloxone was equieffective at reversing OIRD from fentanyl and heroin but was slightly less potent for heroin. Naloxone was equipotent and effective at reversing OIRD from heroin alone and heroin + METH, but less effective at reversing OIRD from fentanyl + METH than fentanyl alone. The rebound tachycardia and tachypnea produced from naloxone reversal of the opioids alone did not differ in magnitude or duration compared to the respective mixture. These findings suggest that unique properties of fentanyl may introduce cardiorespiratory interactions between naloxone reversal of OIRD and the cardiovascular effects of METH (e.g., muscle rigidity exacerbating hypertension from reversal and METH).

Poster 99

Individuals recently abstinent from methamphetamine show selective cognitive and behavioral differences when compared to age-matched controls

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Background: Methamphetamine use disorder (MUD) is associated with deficits in cognitive and behavioral regulation, often conceptualized within the framework of impulsivity. However, the extent to which these deficits align with traditional distinctions between impulsive action and impulsive choice remains unclear. This study aimed to test the hypothesis that individuals with MUD would exhibit greater impairments in response inhibition (impulsive action) compared to decision-making and risk-taking (impulsive choice). Methods: Participants with MUD (n=29) were recruited from 30-day residential treatment programs, along with age-matched controls (n=27). All participants completed the Stop Signal Task (SST) and Stroop Color and Word Task (SCWT) to assess response inhibition, and the Iowa Gambling Task (IGT) and Balloon Analogue Risk Task (BART) to assess decision-making and risk-taking. A multivariate analysis of covariance (MANCOVA) was conducted, controlling for education. Results: Our findings indicated that individuals with MUD had significantly poorer performance on inhibitory control tasks (SST, $p < 0.01$; SCWT, $p = 0.03$) compared to controls, while no significant group differences were observed on the IGT ($p = 0.62$) or BART ($p = 0.45$). Conclusions: These findings suggest that inhibitory control deficits are more pronounced than impairments in risk-based decision-making in MUD, highlighting the need to refine how cognitive processes underlying substance use behaviors are conceptualized.

Poster 100

Triazole 187 is a biased KOR agonist that suppresses itch without sedation and induces anxiolytic-like behaviors in mice

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KOR agonists are clinically used for the treatment of non-histamine-induced itch, or pruritis, while also being pursued as a target in therapies such as pain, anxiety and opioid abuse disorder. Unfortunately, activation of KOR in the central nervous system (CNS) can lead to undesired side effects, such as diuresis, sedation, and dysphoria which has limited the clinical utility of KOR agonists. Biased agonism has been explored as a means to optimize therapeutic properties while avoiding certain side effects. We have previously shown that triazole 1.1 is a G protein signaling-biased KOR agonist, that can suppress itch without producing signs of sedation in mice. This profile was recapitulated in rats and non-human primates however, triazole 1.1 had limited potency as an antipruritic. Here we describe a more potent, G protein signaling-biased agonist, triazole 187. Triazole 187 has improved antipruritic potency compared to triazole 1.1 while avoiding sedation and limiting the extent of diuresis. Triazole 187 produces anxiolytic-like behaviors that are not confounded by sedative properties typically seen in KOR agonists. Compounds like triazole 187 may present a means to treat anxiety accompanied by persistent chronic itch while avoiding sedation and diuresis accompanied by typical KOR agonists.

Poster 101

Enhancing Autism Therapeutics: The Influence of Acute Cannabidiol Treatment and the Estrous Cycle on Social Behavior and Hormone Changes in Adult Male and Female Mice

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent social interaction deficits and repetitive behaviors. Current FDA-approved drugs reduce irritability and aggression but fail to effectively address core symptoms. Additionally, limited research on sex-based differences and hormonal changes complicates treatment in females. Therefore, this study aims to enhance pharmaceutical options that alleviate core ASD symptoms while investigating sex-specific treatment complexities. Cannabidiol (CBD), a nonintoxicating constituent of Cannabis sativa, has shown promise in alleviating ASD social deficits. The estrous cycle, a four-stage reproductive cycle in female mice, causes hormonal fluctuations that introduce behavioral complexities. We hypothesized that an acute 15 mg/kg CBD dose improves social behavior in adult BTBR and C57BL/6 mice, and that hormone changes during the estrous cycle influence social behavior. CBD's impact on autism-relevant behaviors was evaluated using social interaction sniffing, social novelty sniffing, marble burying, and a social dominance tube test. Additionally, fecal boli were counted to assess anxiety. Macroscopic and microscopic analyses were performed to determine estrous cycle stages, and hormone assays quantified estradiol and progesterone concentrations in blood samples. Significant behavioral effects were observed in marble burying, number of fecal boli, tube test wins, and tube test duration. In female mice, higher estradiol levels correlated with increased social novelty, and higher progesterone levels correlated with reduced repetitive behavior. These findings demonstrate that CBD has the potential to improve ASD core symptoms and that reproductive hormone fluctuations influence behavioral outcomes.

Poster 102

Effects of repeated alprazolam (Xanax) exposure during adolescence on mood-related behaviors and stress susceptibility

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Reports show that alprazolam (Xanax; ALP) is the most abused benzodiazepine (BZD) among adolescents. In adults, repeated exposure to BDZs can lead to adverse effects including a rebound of anxiety during periods of abstinence. Given that adolescence is a sensitive period of development marked by heightened sensitivity to stress and drugs use/abuse, this study was designed to investigate the effects of repeated ALP exposure on stress susceptibility and responsivity to environments inducing anxiety- and depression-like behaviors. Adolescent male mice (postnatal day [PD] 35) were exposed to vehicle (VEH) or ALP (0.5 mg/kg) once daily from PD 35-49, and were then tested on various behavioral assays (i.e., open field test [OFT], three-chamber sociability test, elevated-plus maze [EPM], and the forced swim test [FST]) 24-h (short-term; ST) or 1-month (long-term; LT) after drug cessation. In a separate cohort, mice received ALP as described and then subjected to chronic social defeat stress (CSDS) after drug cessation to assess their sensitivity to stressful circumstances. In the ST groups, we observed significant increases in time spent in the center of the OFT and social interaction and decreases in immobility in the FST (no stress susceptibility) when compared to VEH-treated controls. In the LT groups, we observed significant increases in social interaction and increases in time spent immobile in the FST (stress susceptibility) when compared to VEH-treated controls. Our results indicate that repeated ALP treatment during adolescence dysregulates mood-related behaviors in the LT that can profoundly influence susceptibility to stressful circumstances in adulthood.

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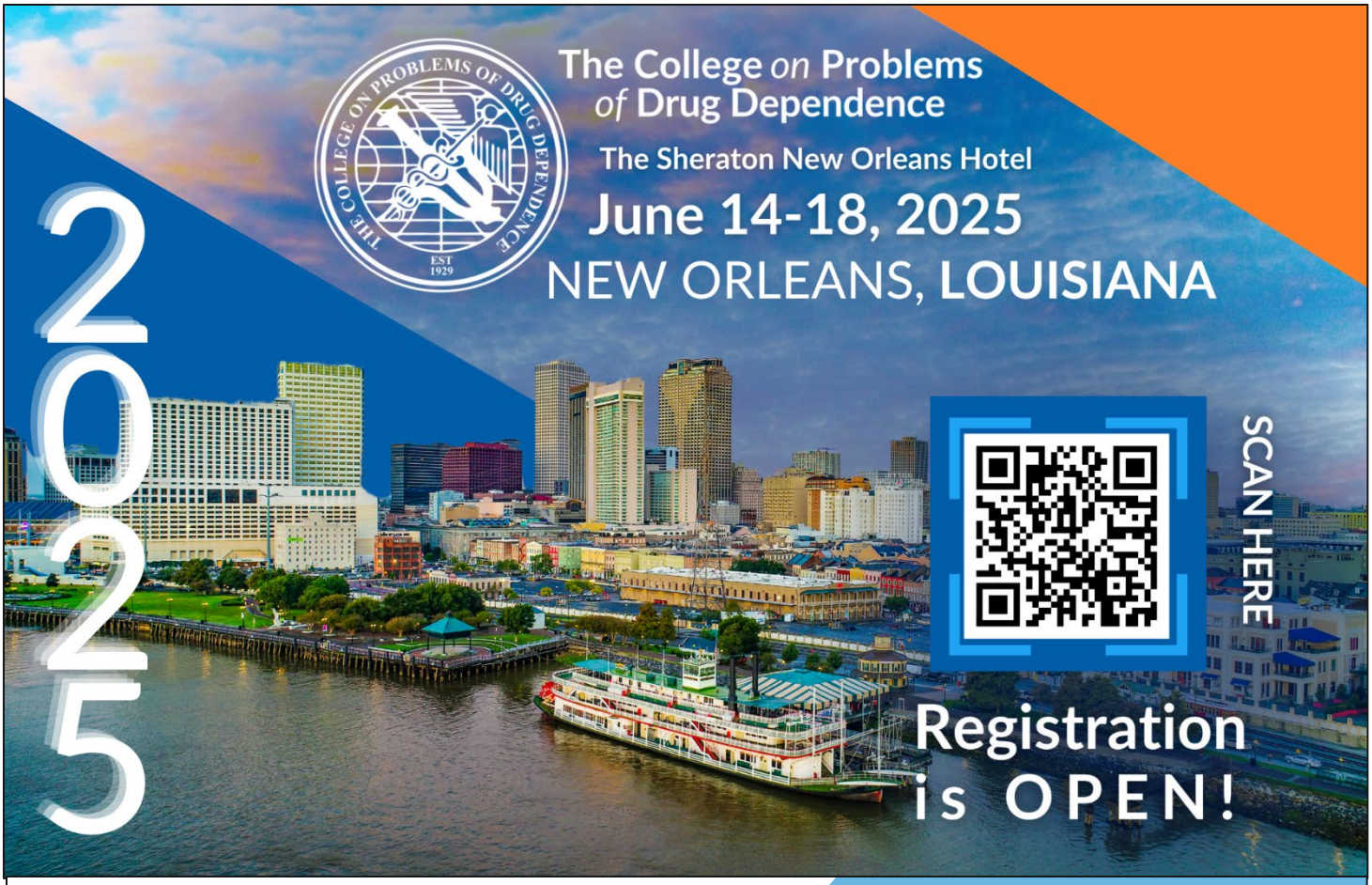

JOHNS HOPKINS CAREY BUSINESS SCHOOL | **Executive Education**

INNOVATIONS FOR SUBSTANCE USE DISORDERS (I4SUD) PROGRAM

I4SUD

Duration of the Program
October 13 - December 5, 2025 (only 4 days in person)

Description of the Program

I4SUD is an Executive Education certificate program offered to select applicants for free through Johns Hopkins Carey Business School (JHU CBS). The program will enroll 30 researchers who are motivated to solve challenges related to substance use disorders (SUDs). During the program, participants will work individually or with their team to assess if their pharmaceutical, digital health, or medical device-related inventions can be transformed into innovations to address problems in SUDs. I4SUD combines asynchronous and synchronous online activities; a multi-day sponsored trip to JHU CBS in Baltimore, MD, for workshops led by world-class faculty, visits to operational SUD programs, netowrking/community building, including meeting NIDA program officers, and the development of a commercialization plan to make participants competitive for follow-on funding opportunities.

Expected Commitment

- Attend **4 full days** in person in Baltimore, MD (October 21 - 24, 2025)
- Attend **three virtual sessions**, 1.5 hours each (Wednesdays, 12 PM - 1:30 PM ET on October 15, November 5 & 19, 2025)
- Attend **at least two** 30 min virtual office hour or clinic sessions with mentors or instructors (Wednesdays, 12 - 1:30 PM ET on October 29, November 12 & December 3, 2025)
- Engage in **3-4hrs per week** of asynchronous learning activities between October 13 and December 5, 2024, and spend time on research to develop their pitch (dependent on participant idea and stage)
- Attend and pitch in the virtual pitch competition from **1 PM - 4 PM ET on December 5, 2025** with a chance to win $10,000!

Notes

Notes

Poster Index

Maharaj ("Raj") Ticku, PhD

Dr. Maharaj ("Raj") Ticku was born in India. In 1970, after graduating with Honors in Pharmacy from the Birla Institute of Technology and Science in Pilani, he moved to the United States, subsequently receiving an MS in Pharmacology from the University of Oklahoma and a PhD in Biochemical Pharmacology from the State University of New York, Buffalo. Raj then joined the laboratory of Dr. Richard Olsen at the University of California Los Angeles where he began his pioneering work on γ-aminobutyric acid (GABA) and *N*-methyl-D-aspartic acid (NMDA) receptors. In 1978, he joined the Department of Pharmacology at the University of Texas Health Science Center at San Antonio where he rapidly rose through the ranks to professor (Pharmacology and Psychiatry).

Raj was truly a pioneer in pharmacology and alcohol abuse research. He was always on the cutting edge of research on GABA and NMDA receptor expression, trafficking, and phosphorylation and his work continues to have a major impact on our understanding of receptor signaling and the neuropharmacology of alcohol. In 1980, he published a paper entitled "*The effects of acute and chronic ethanol administration and its withdrawal on gamma-aminobutyric acid receptor binding in rat brain*" which laid the groundwork for the next several decades of research on the mechanisms of action of alcohol. Another seminal contribution was a 1981 paper on "*Histidine modification with diethyl pyrocarbonate shows heterogeneity of benzodiazepine receptors,*" in which he predicted what receptor cloning and sequencing would require another decade to unravel, that the α-subunits of the GABA-A receptor vary in a critical histidine that determines their drug sensitivity. Raj continued to expand his interests and expertise throughout his career. When it became a popular drug of abuse in the early 2000s, he characterized the mechanism of action of γ-hydroxybutyric acid and shortly before his passing, he was awarded a new grant to use then state-of-the-art epigenetic approaches to study the heritability of alcoholism.

Raj served on numerous National Institutes of Health (NIH) study sections and as a referee for many prestigious national and international scientific journals. Throughout his career, he was exceptionally well supported by the NIH including a prestigious MERIT award from the National Institute on Alcohol Abuse and Alcoholism. Raj's research was of the highest quality, he was very prolific, publishing more than 180 original manuscripts, and 24 invited book chapters.

Raj was known for his enthusiasm, his distinct laugh, his love for and extensive knowledge of different foods and cuisines, and above all his inquisitiveness of science and respect for his fellow scientists. In memory of Raj's many significant contributions to addiction research, each year an investigator who is not more than 4 years beyond postdoctoral training is awarded the ***Maharaj Ticku Memorial Travel Fellowship for New Investigators*** to attend and make an oral presentation at the annual meeting of ***Behavior, Biology and Chemistry: Translational Research in Substance Use Disorders***.

Maharaj Ticku Memorial Travel Fellowship for New Investigators

2012 – Jun-Xu Li	2013 – Kevin B Freeman	2014 – Christopher W Cunningham
2015 – Brian D Kangas	2016 – Clinton E Canal	2017 – Thomas M Keck
2018 – Comfort A Boateng	2019 – Stephen J Kohut	2020 – Lee Gilman
2022 – Corinde E Weirs	2023 – Justin C Strickland	2024 – Zijun Wang
2025 – Jacques D Nguyen		