UC College of Medicine Center for Addiction Research (CAR) Summer Speaker Series

Sponsored by: Center for Addiction Research

July 9, 2025
12:00 – 1:00PM

This event is being recorded.

Participants can enable captions in the taskbar under more.

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Center for Addiction Research (CAR)

- The CAR was launched in October of 2020
- Mission: to support cross-disciplinary collaborations across UC as well as with community partners, governmental institutions, and other academic institutions in order to accelerate scientific progress in addiction prevention and treatment
- Thirty-two faculty from six UC Colleges
- CAR Website: https://med.uc.edu/institutes/CAR/home

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CAR Website

- Publications:
  https://med.uc.edu/institutes/CAR/publications
- Projects:
  https://med.uc.edu/institutes/CAR/projects
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- To become an affiliate member:
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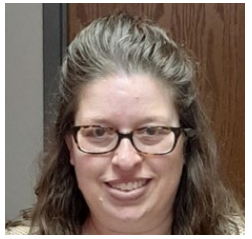
The COM CAR Summer Speaker Series

- Special thank you for planning and operational assistance from:
  - Jen Rowe - Assistant to Dr. T. John Winhusen



  - Jermaine Fields – UI/UX Lead, UC DTS Application & Software Development/ COM Web Development

  - Todd Schutter –Multi-Media Coordinator, UC DTS COM

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Endocannabinoid regulation of repeated stress-cocaine interactions

Jayme McReynolds, PhD
Assistant Professor
Department of Pharmacology, Physiology, and Neurobiology
University of CINCINNATI

Learning Objectives

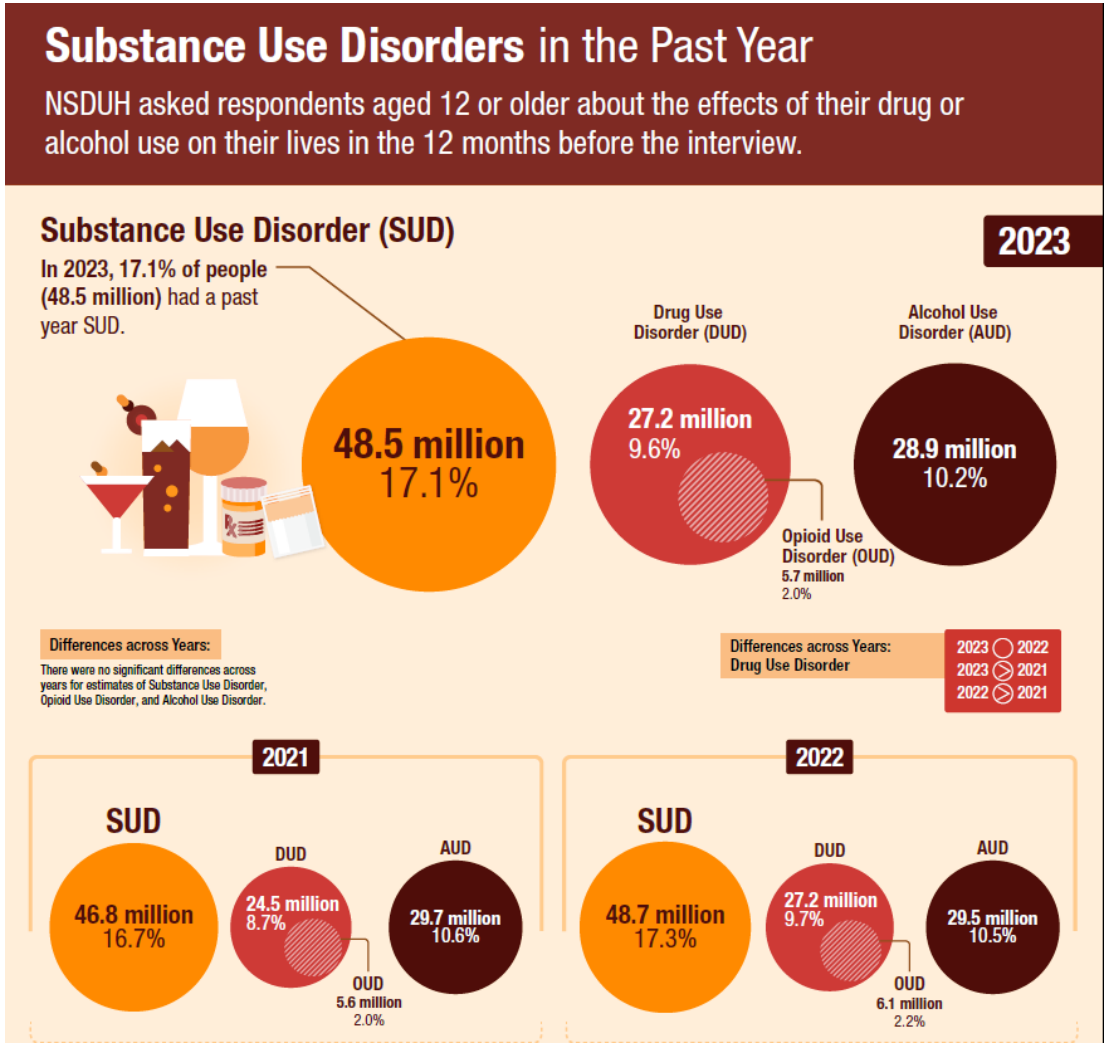
1. Understand how we can use preclinical models to study aspects of substance use disorders.

2. Discuss the importance of integrating environmental factors such as stress into preclinical models.

3. Appreciate the potential involvement of stress in unique neurobiological mechanisms underlying substance use disorders.

4. Review the potential of the endocannabinoid system as a therapeutic target in treating cocaine use disorder.

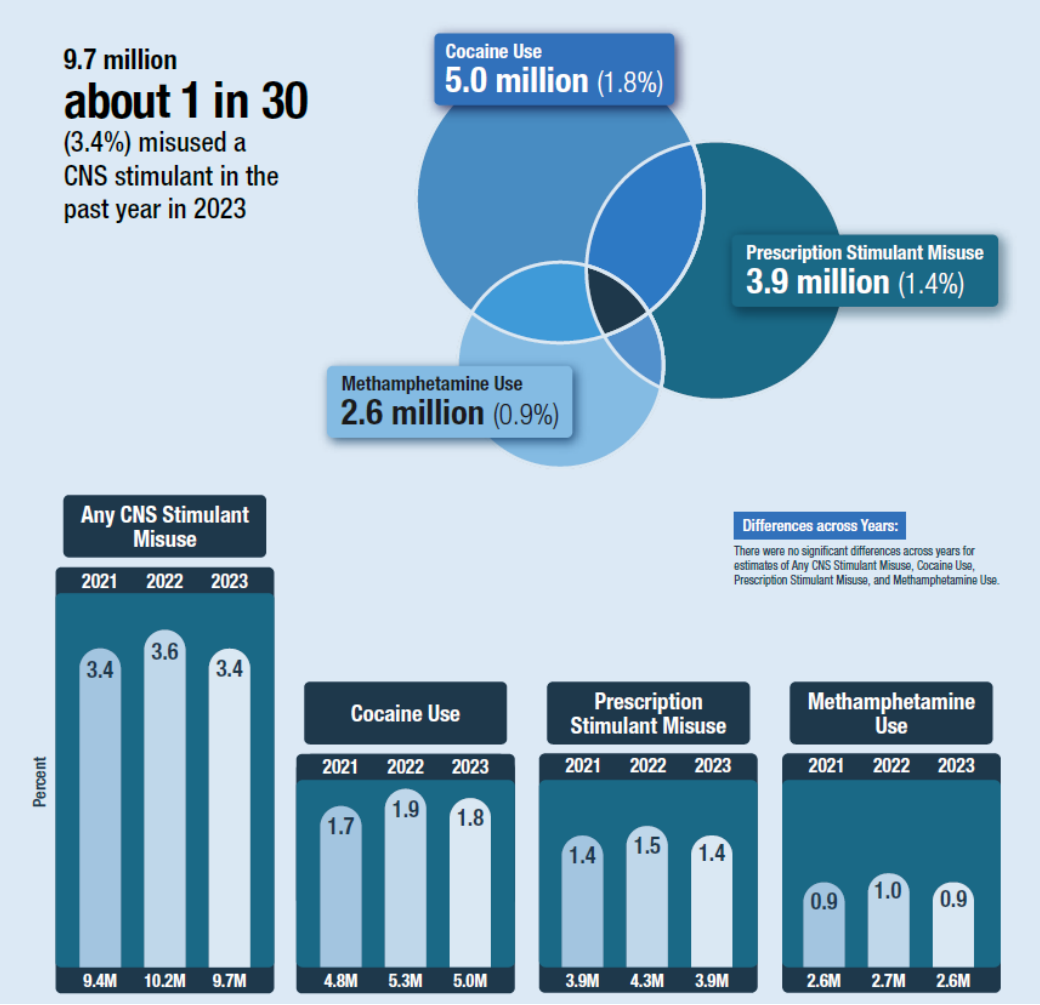
The problem of addiction



2023 Companion Infographic Report, NSDUH 2023

- 48.5 million Americans have a substance use disorder for illicit substances or alcohol (NSDUH, 2023).

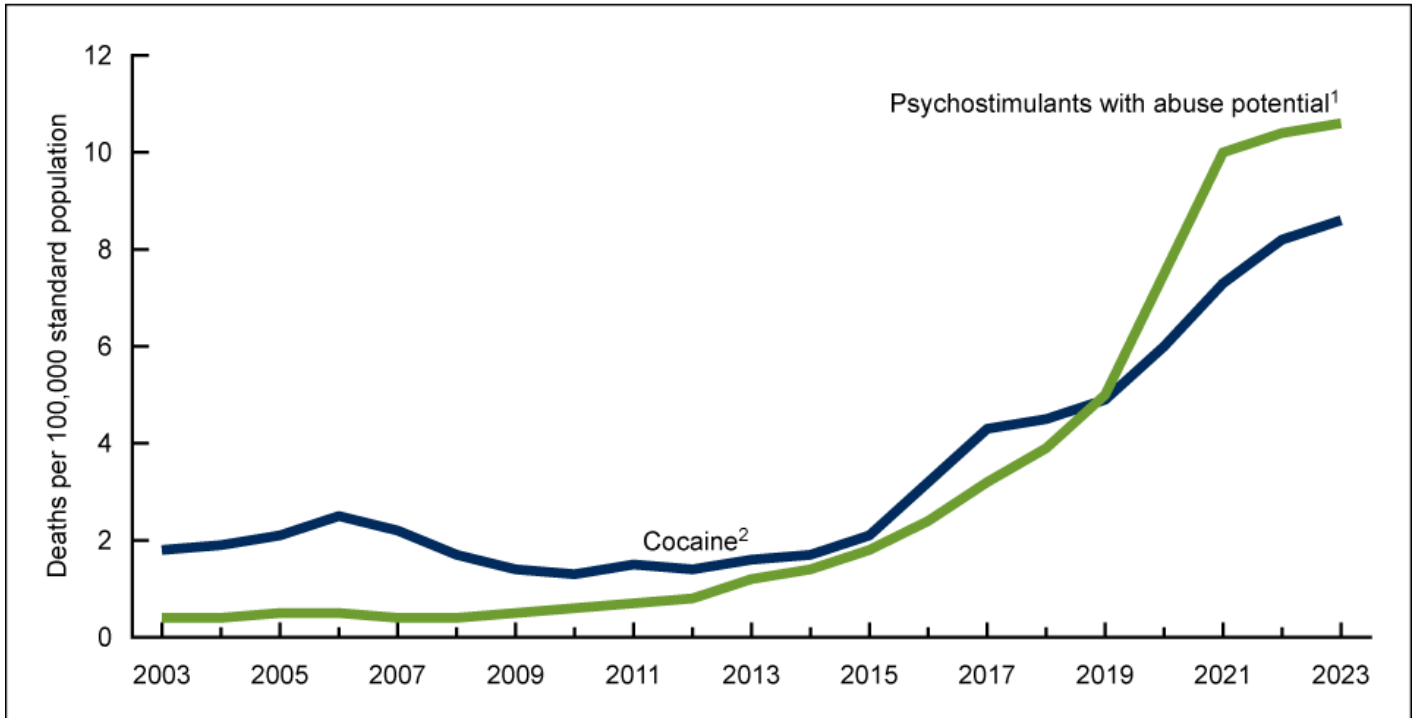
The problem of addiction



- 48.5 million Americans have a substance use disorder for illicit substances or alcohol (NSDUH, 2023).
- 5.0 million Americans have misused cocaine in the past year (NSDUH, 2023)
- 1.3 million Americans had a past year cocaine use disorder (NSDUH, 2023)
  - Over half of those were classified as having a moderate (22.4%) or severe (41.9%) substance use disorder
  - This is associated with serious consequences for their physical, social, and economic wellbeing

2023 Companion Infographic Report, NSDUH 2023

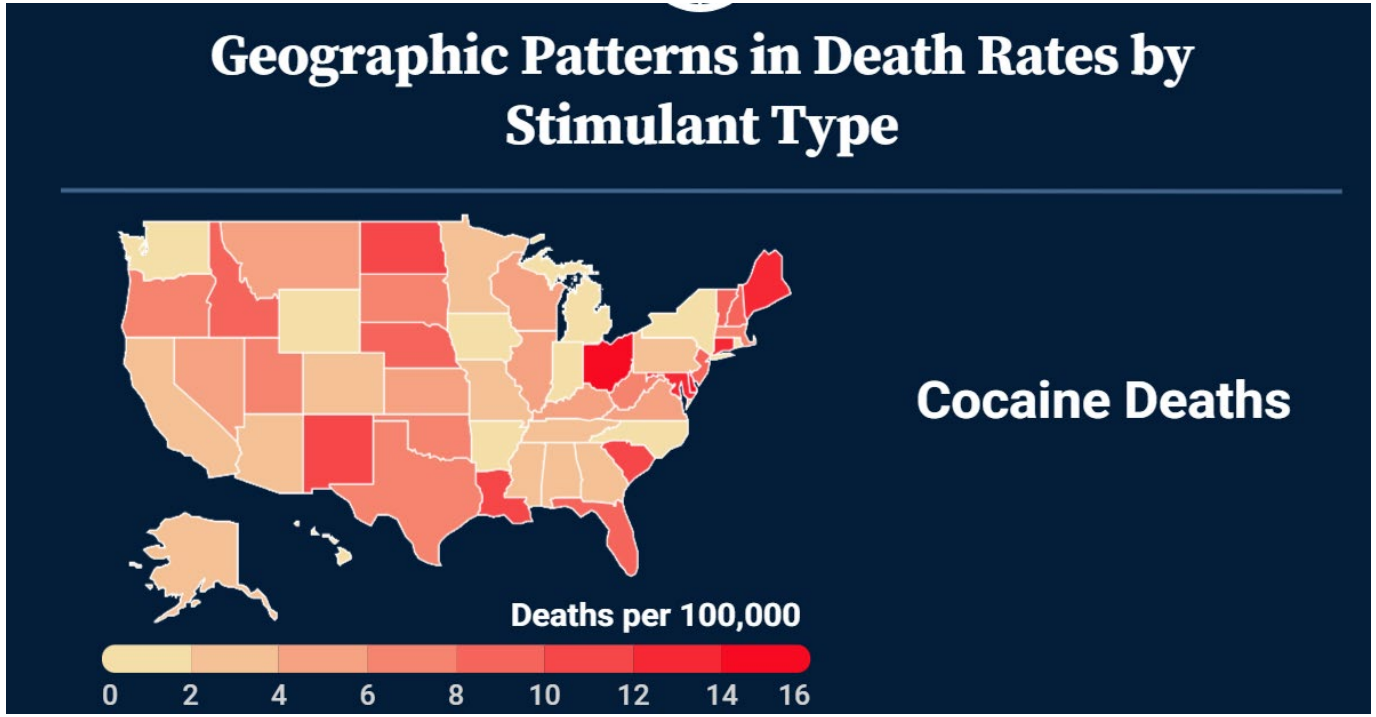
The problem of addiction



- The number of overdose deaths involving cocaine has been on the rise
  - 1.3 deaths per 100,000 people in 2010
  - 8.6 deaths per 100,000 people in 2023

National Center for Health Statistics, 2024

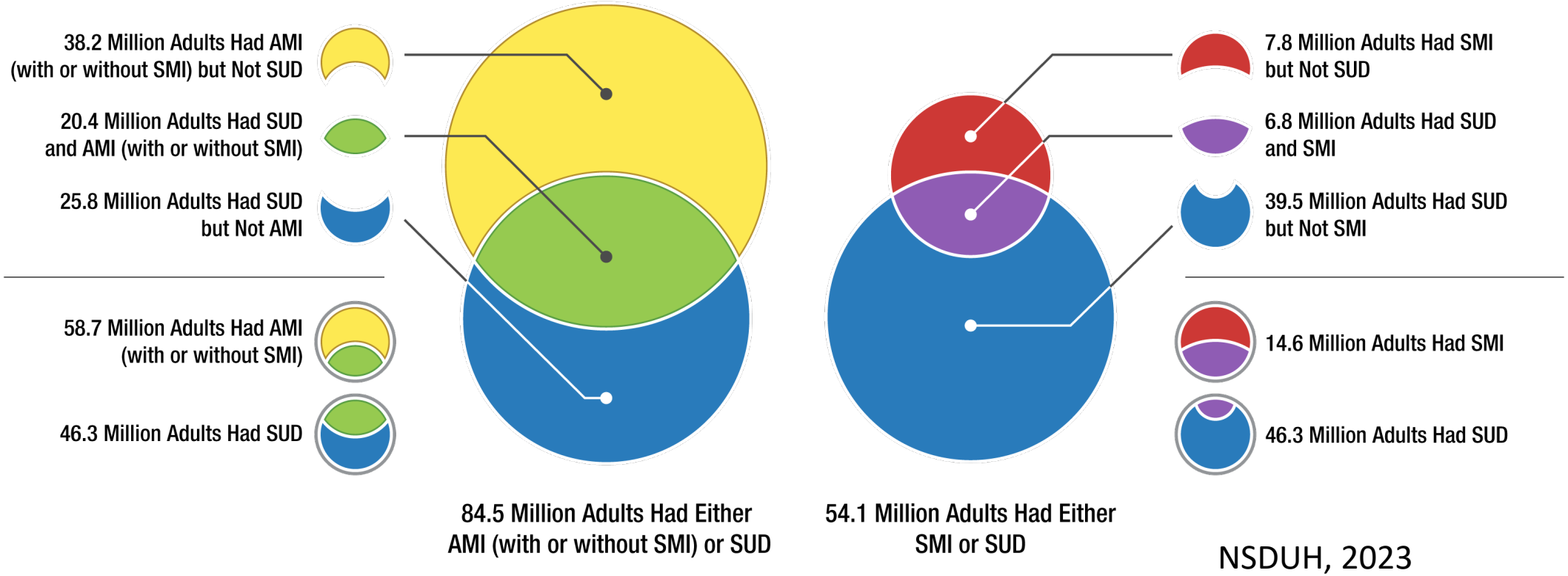
The problem of addiction



NIHCM Foundation, 2022 – Charting the stimulant overdose crisis & the influence of fentanyl

- The number of overdose deaths involving cocaine has been on the rise
  - 1.3 deaths per 100,000 people in 2010
  - 8.6 deaths per 100,000 people in 2023
- In 2020, Ohio had the highest cocaine overdose death rate – 17.8 per 100,000
- There is no FDA-approved medication for the treatment of cocaine use disorder making this a critical unmet need
- Need to better understand the neurobiological processes that underlie relapse and drug use to develop better behavioral and pharmacological therapies.
  - For better translation of bench to bedside we need to incorporate factors beyond the drug itself such as sex, genetics, polysubstance use, **stress**

Stress and Addiction



NSDUH, 2023

- High incidence of anxiety/mood disorders in people with cocaine use disorder (Rounsaville et al, 2001; Chen et al, 2011).

Stress and Addiction

- Stress in a lab setting induces drug craving, including craving for cocaine (Sinha et al, 2009).
- Link between cocaine use/CUD and post-traumatic stress disorder (PTSD; Back et al, 2006; Waldrop et al, 2007; Burns et al, 2010; Goodrum et al, 2022; Hull et al, 2025).
- Cocaine users have higher basal levels of stress hormones and there is a link between stress or cortisol levels and cocaine use/future recurrent use (Sinha et al, 2000; Sinha et al, 2006; Waldrop et al, 2007; Wemm & Sinha, 2019; Voegel et al, 2022).
- Early life stress/trauma serves as a strong predictor for later development of drug dependence (Brown et al, 1995; Hyman et al, 2008; Enoch 2011; Khoury et al, 2010).
- Stress has the ability to influence the development, progression, and severity of CUD

How to study drug-related behaviors using rodents

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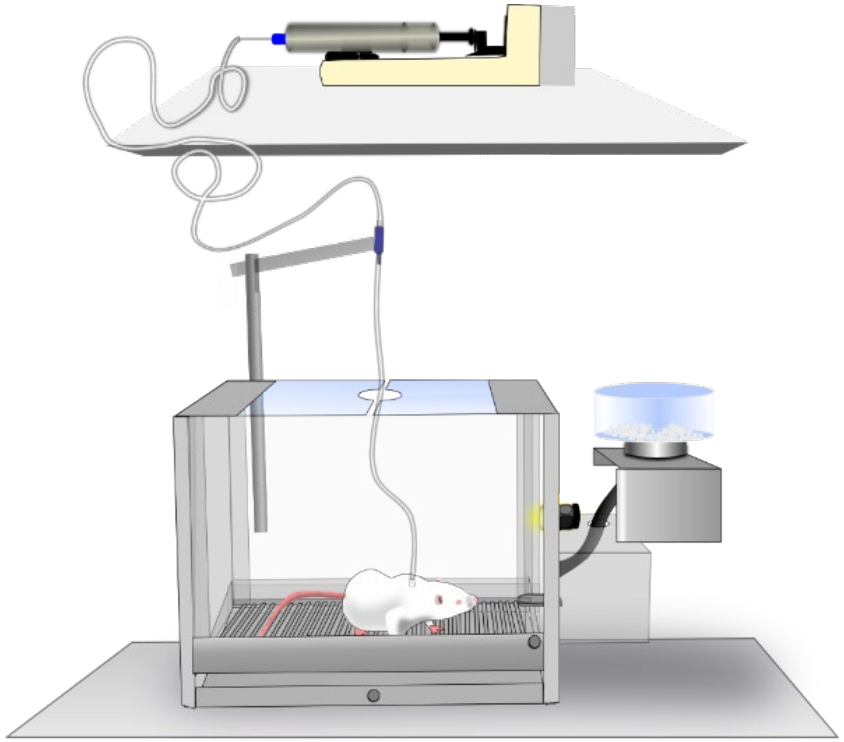
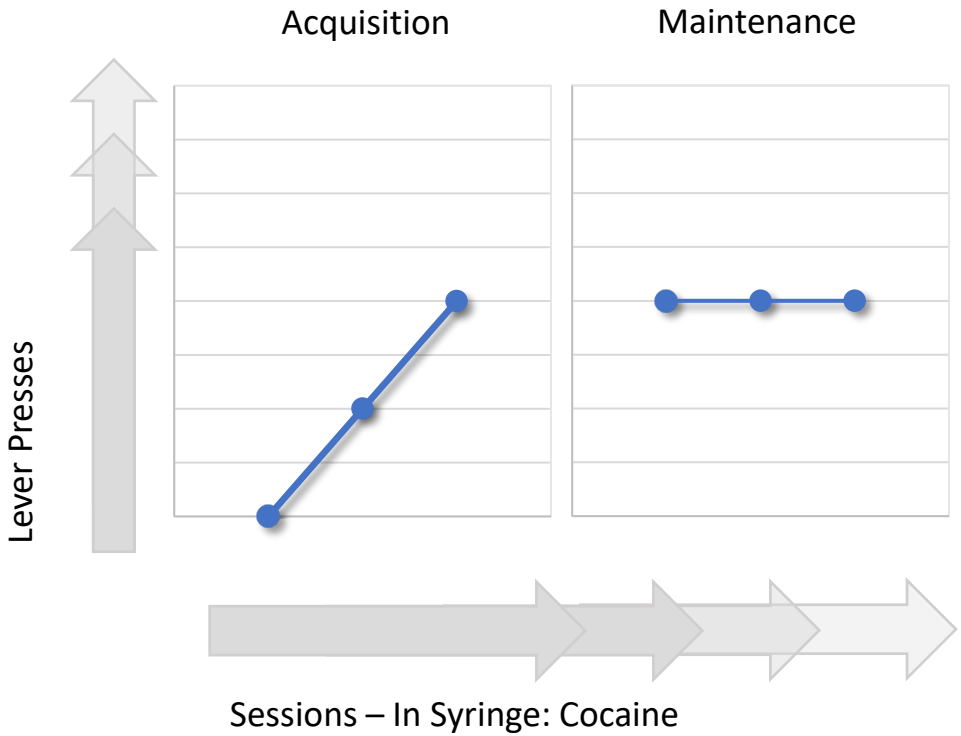
Cocaine Self-Administration (SA)



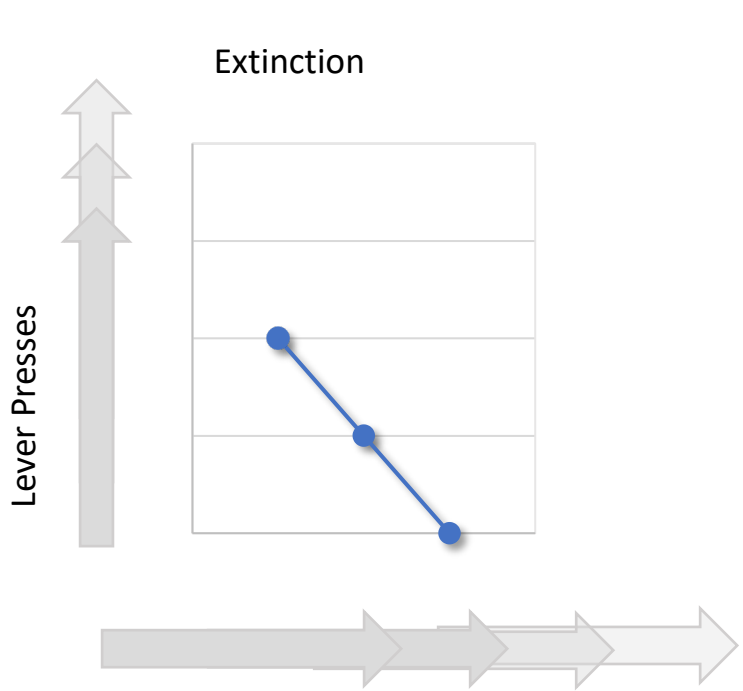


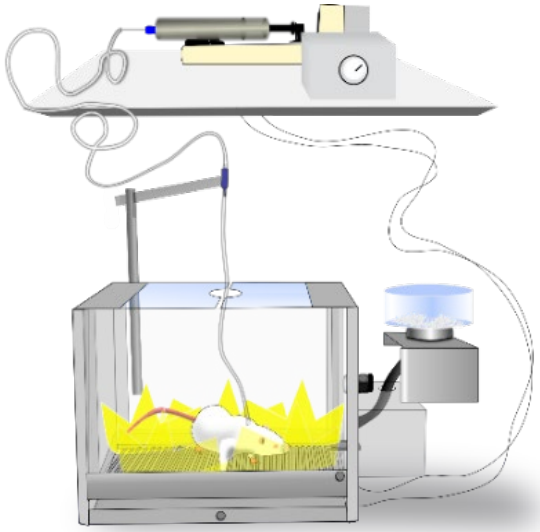
Sprague-Dawley rats

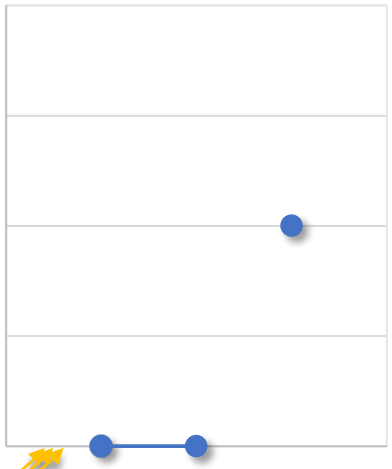
Cocaine was self-administered (0.5 mg/kg/.2 mL infusion) 14 x 2hrs/days on a FR4 schedule.

Figure by Dr. David Peña

Extinction/Reinstatement model of drug-seeking behavior







Reinstating stimuli:
Stress (Footshock, yohimbine)
Cocaine prime

Why use an extinction approach? Extinction training engages brain circuits that are known to be altered in human SUD

Can stress drive cocaine-taking behavior?

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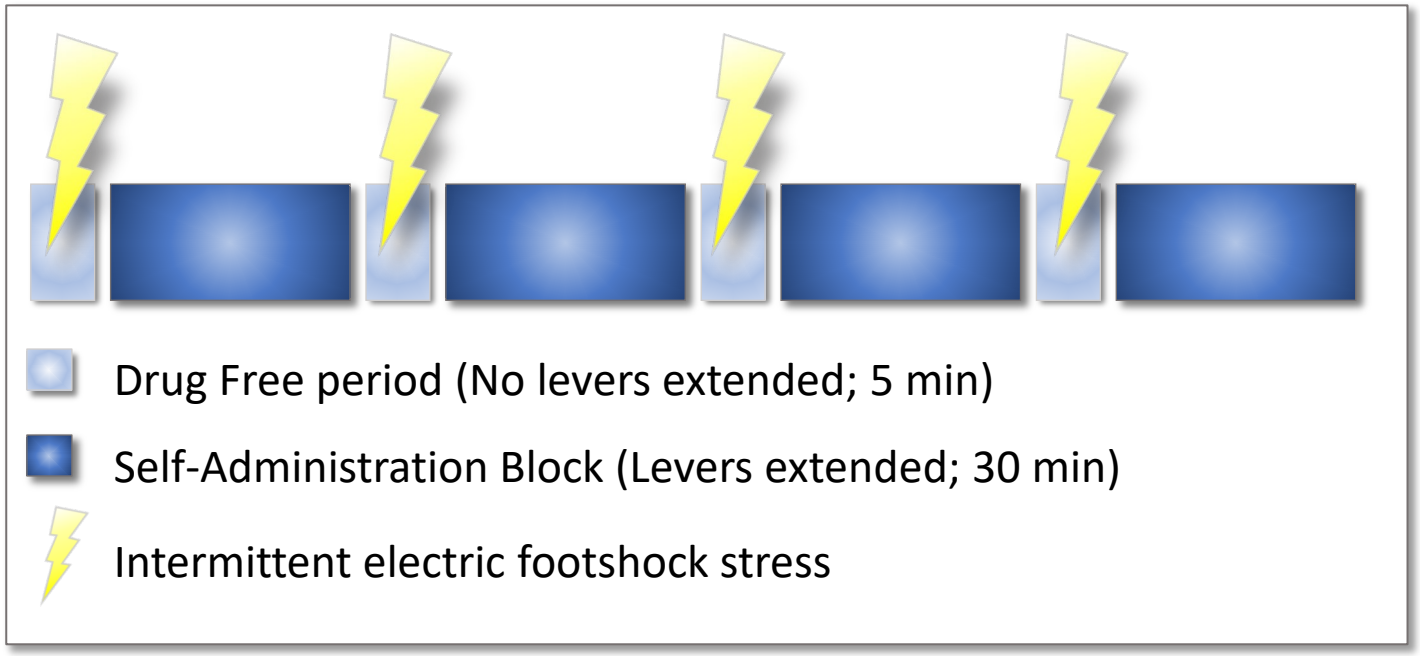
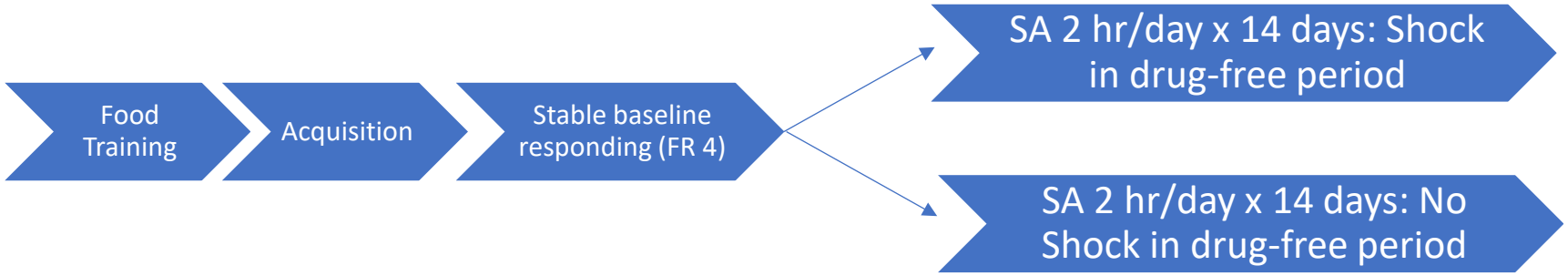
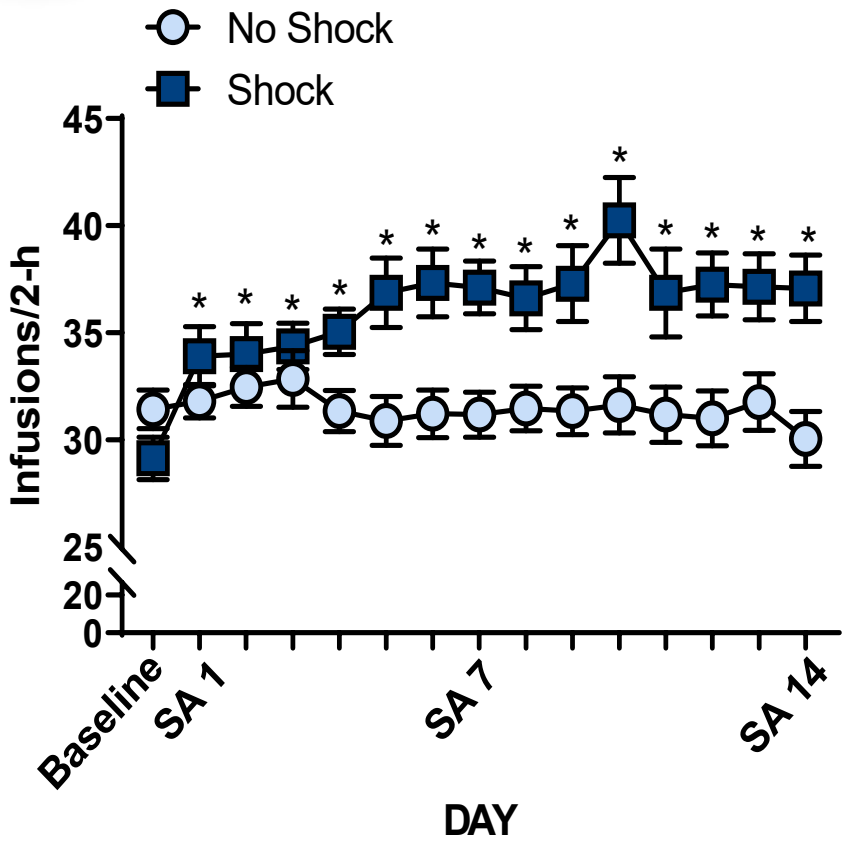
Stress-induced enhancement of cocaine SA: modified short-access program

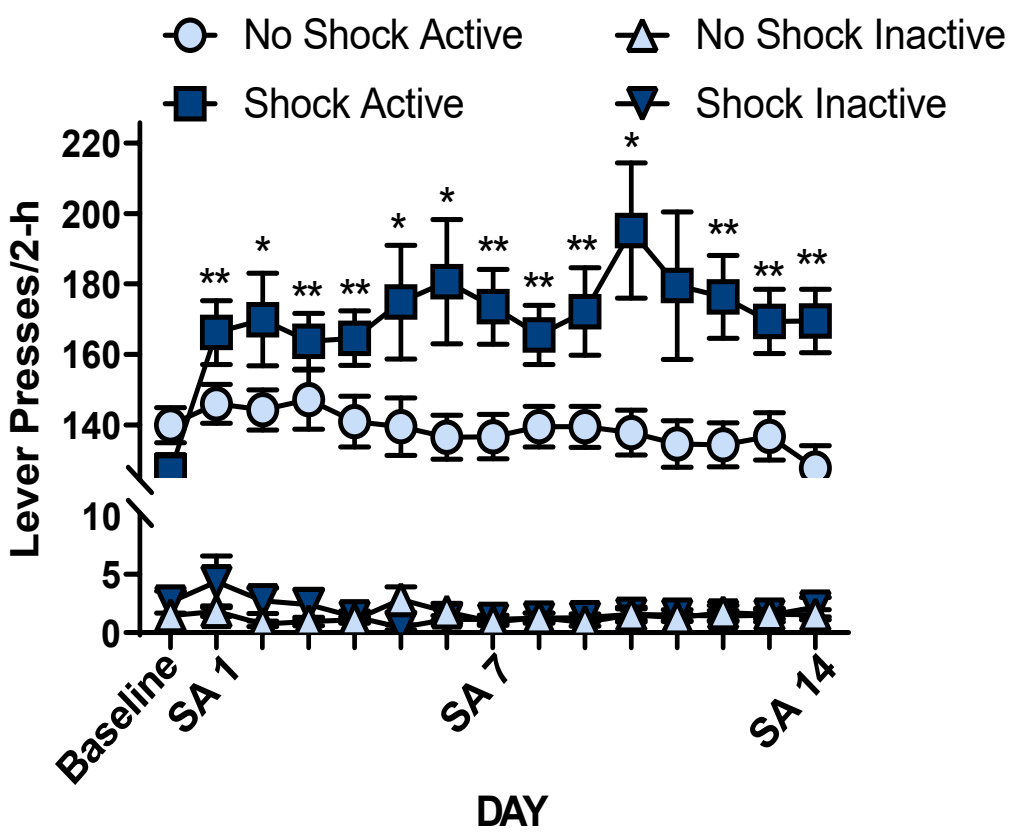




Intermittent electric footshock: 3 x 0.5 mA, 500 msec duration, 1 sec intershock interval, 30 sec average inter-triplet shock interval, range 15-60 sec

Electric footshock stress induces an enhancement of cocaine SA





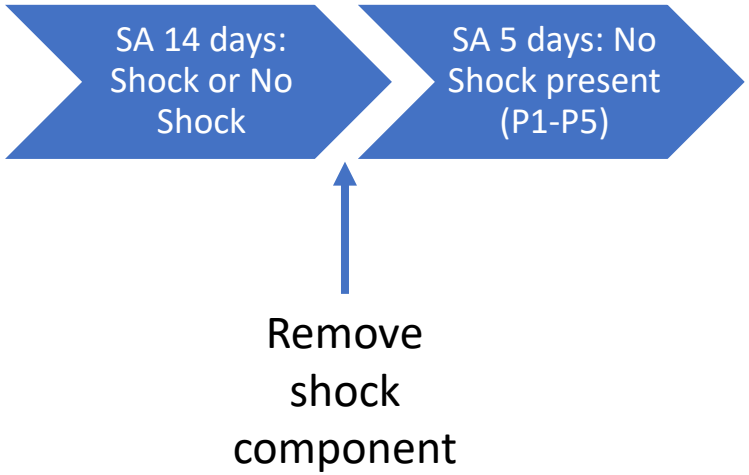
Stress-induced enhancement of cocaine intake is glucocorticoid-dependent and both context- and time-dependent (Mantsch & Katz, 2007)

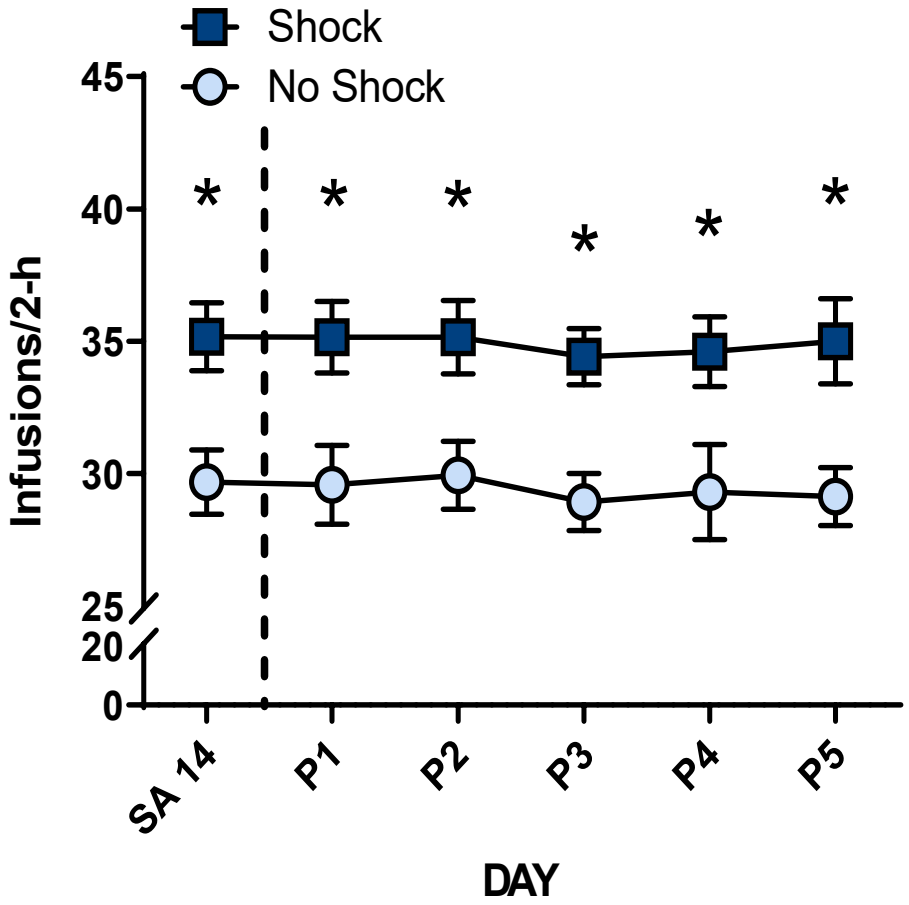
*p<.05, compared to No Shock

McReynolds et al, 2023 *NPP*

Is stress-enhanced cocaine SA the result of persistent neuroadaptations?

Repeated daily stress results in persistent increases in cocaine SA even in the absence of stress





McReynolds et al, 2023 *NPP*

Are the stress-induced neuroadaptations long-lasting?

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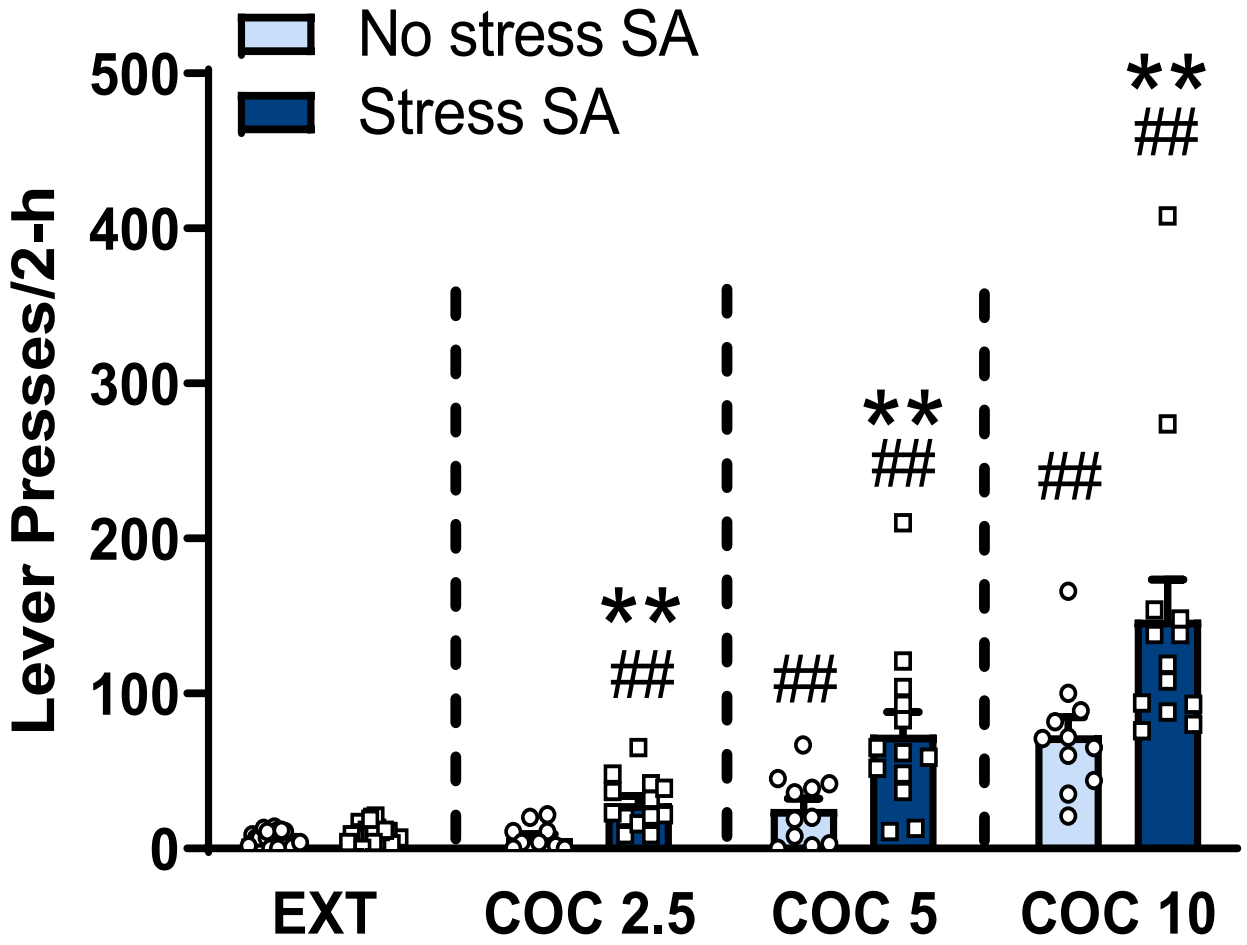
Rats with a history of combined repeated stress and cocaine SA show increased cocaine-primed reinstatement



Reinstatement – Cocaine (2.5, 5, 10 mg/kg, i.p.)

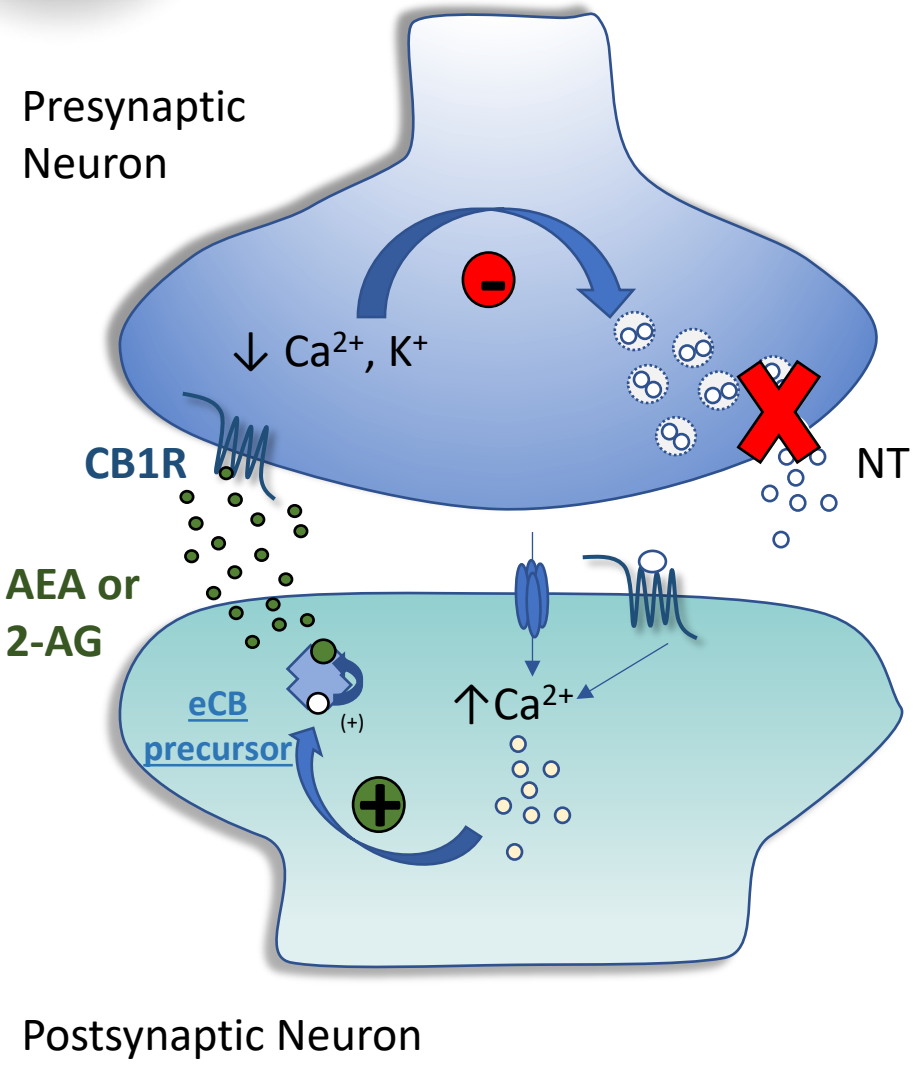
Rats with a history of stress also show increased stress-induced reinstatement

##p<.01, compared to EXT; **p<.01, compared to No Stress SA

McReynolds et al, 2023 *NPP*

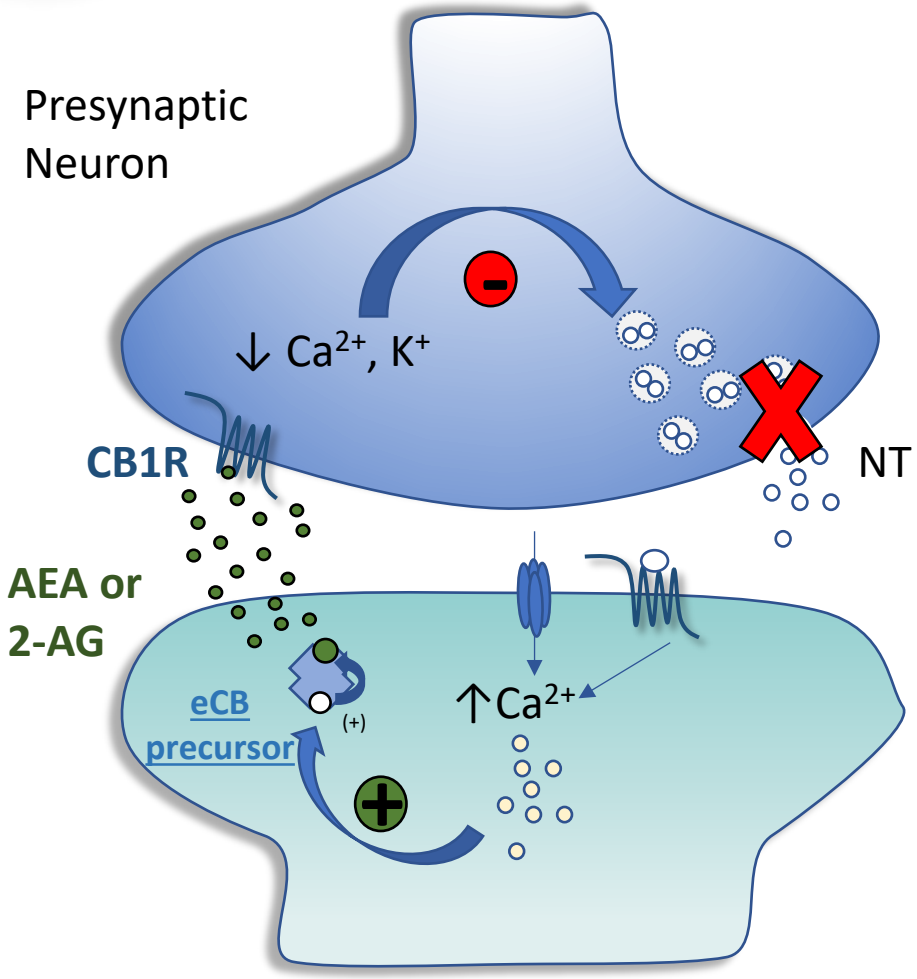
What are the stress-induced neuroadaptations?

Endocannabinoid signaling

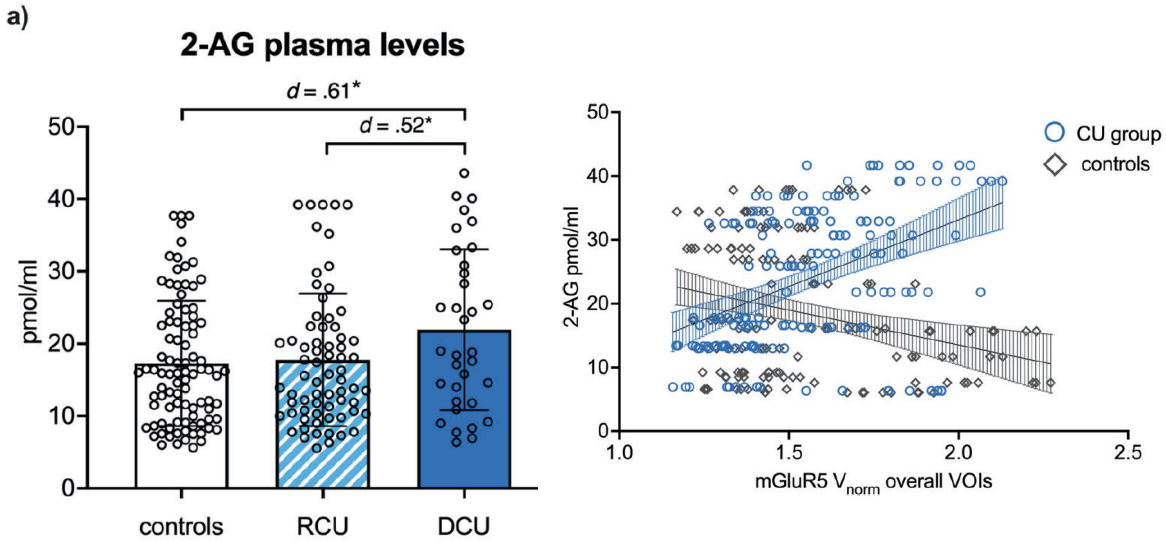


- Anandamide (AEA) and 2-AG are synthesized post-synaptically in response to neuronal depolarization
- AEA and 2-AG are retrograde messengers that bind to $G_{i/o}$- coupled CB_1 receptors.
- Activation of CB1Rs results in inhibition of pre-synaptic neurotransmission.
- CB1Rs are located on glutamatergic and GABAergic neurons.

Endocannabinoid involvement in addiction

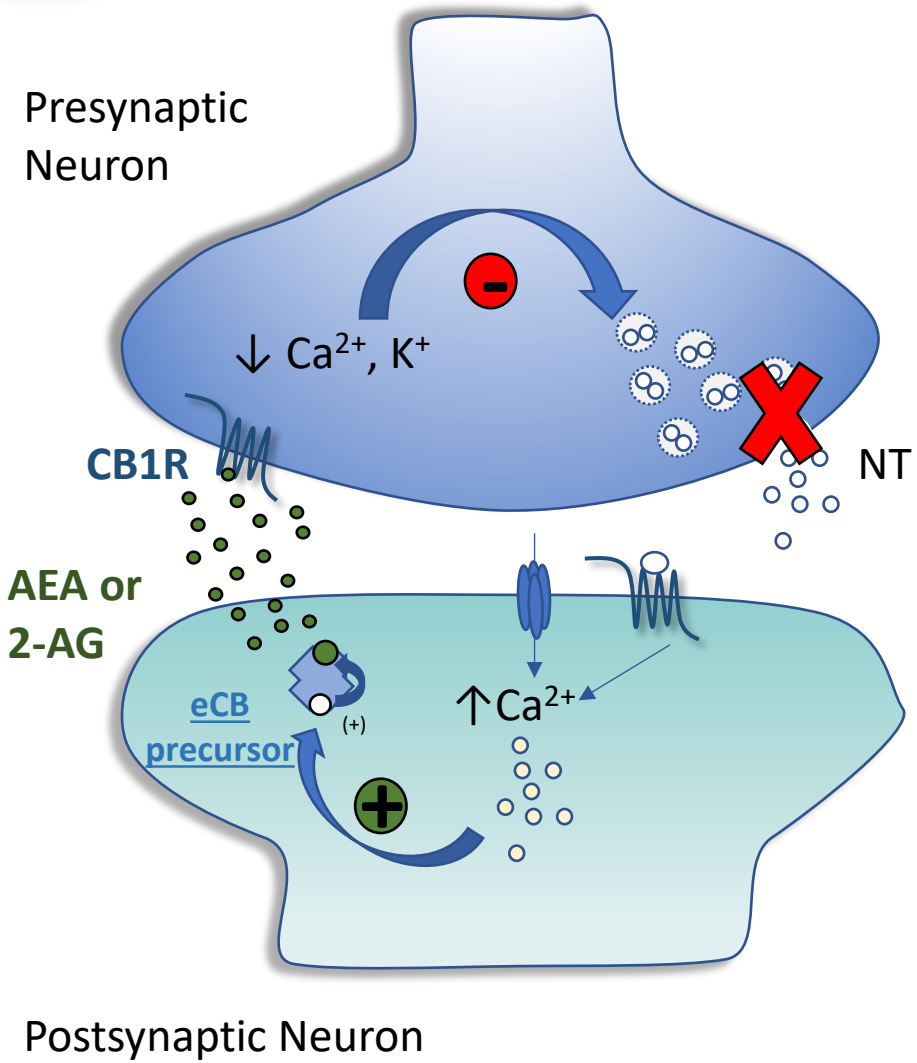


- Polymorphisms in the human gene for the CB1R, *CNR1*, are associated with cocaine dependence (Clarke et al. 2013; Lopez-Moreno et al. 2012; Zuo et al. 2007; Zuo et al. 2009).



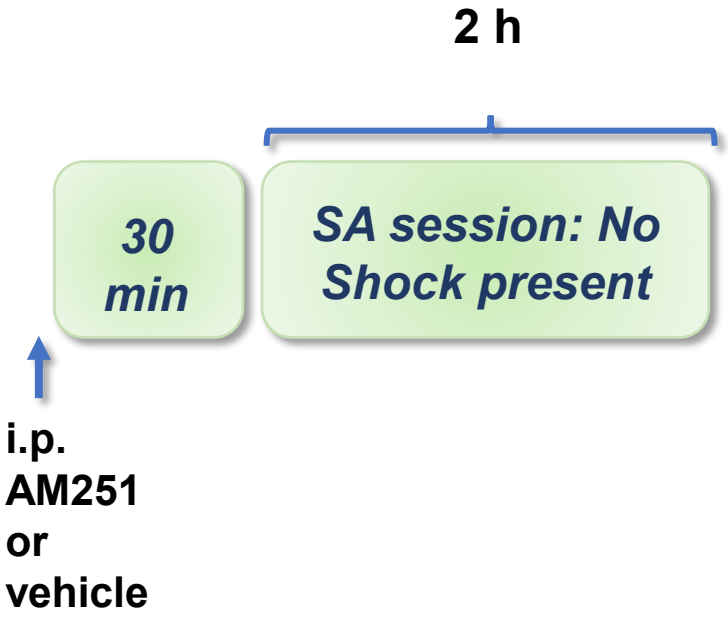
Kroll et al, 2023 *Transl Psych*

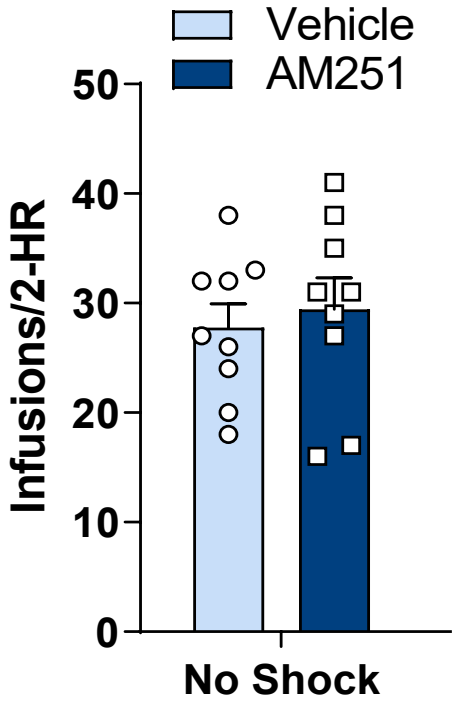
Endocannabinoid involvement in addiction



- CB1R activation has been implicated in cocaine-related behaviors in rodents, such as locomotor sensitization and cocaine-related memory tasks.
- However, the effects of CB1R activation on cocaine SA/RST under non-stress conditions is inconsistent, but . . .
- Endocannabinoids are regulated by both acute and chronic stress in reward- and stress-related brain regions.
- Endocannabinoid signaling may be involved in cocaine SA/RST under conditions involving stress (McReynolds et al, 2016; McReynolds et al, 2018)

CB1R antagonism attenuates cocaine SA only in rats with a history of stress





AM251 (1 mg/kg, i.p.) – CB1R antagonist

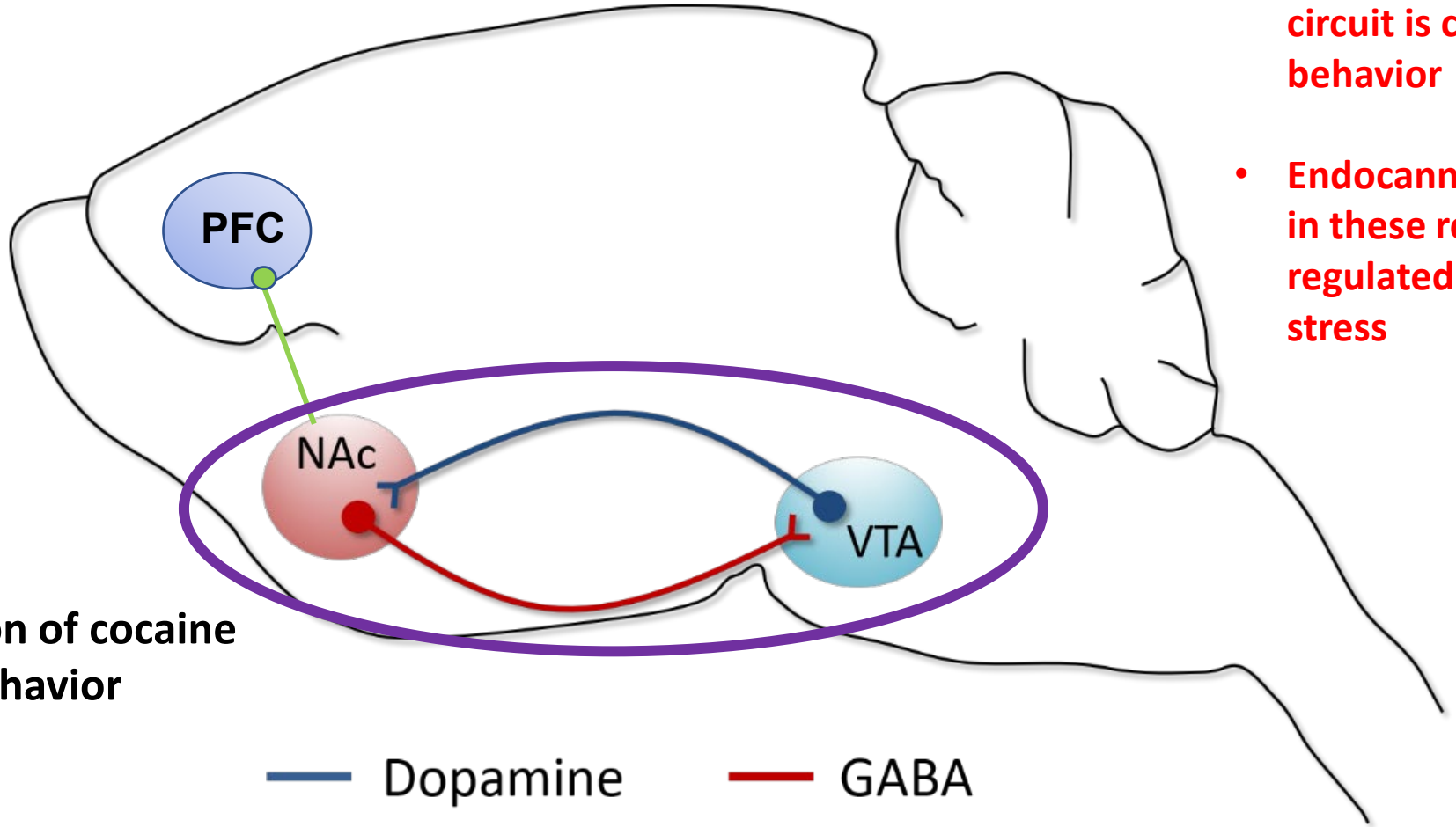
#p<.05, compared to No Shock; **p<.01, compared to Veh

McReynolds et al, 2023 *NPP*

Where are the stress-induced neuroadaptations?

Regulation of endocannabinoids in regions critical for drug-taking behavior

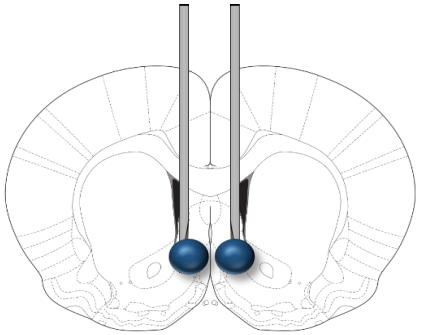
- **Dopamine release in this circuit is critical for SA behavior**
- **Endocannabinoid signaling in these regions is regulated by cocaine or stress**

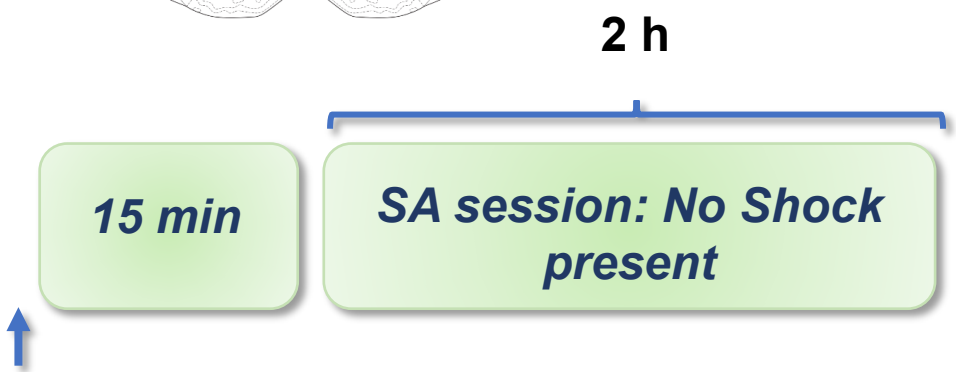


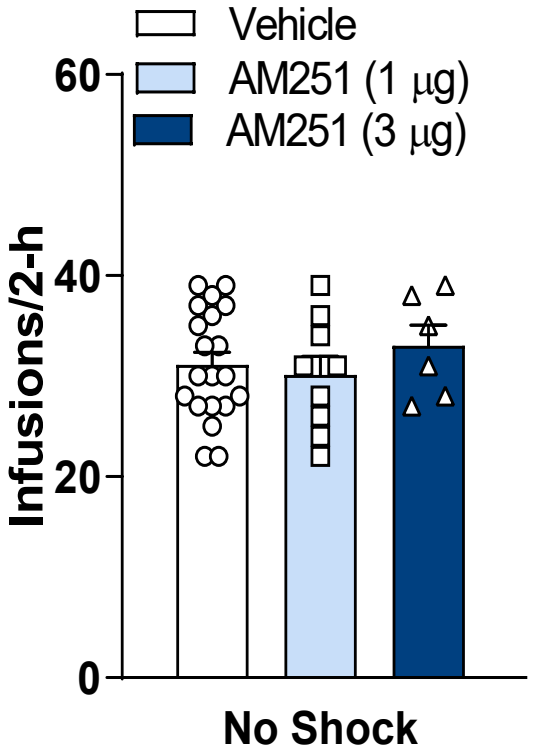
Regulation of cocaine taking behavior

Intra-NAc shell administration of a CB1R antagonist attenuates cocaine SA

Acquisition → Stable Baseline responding → SA 2-h/day x 14 days → Remove stress component & test







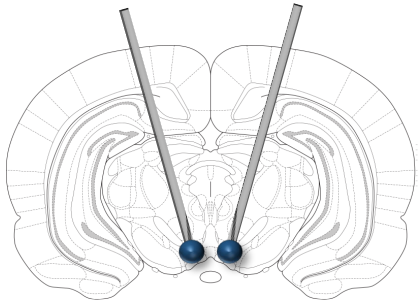
AM251 (0, 1, or 3 µg/0.3 µL) – CB1R antagonist

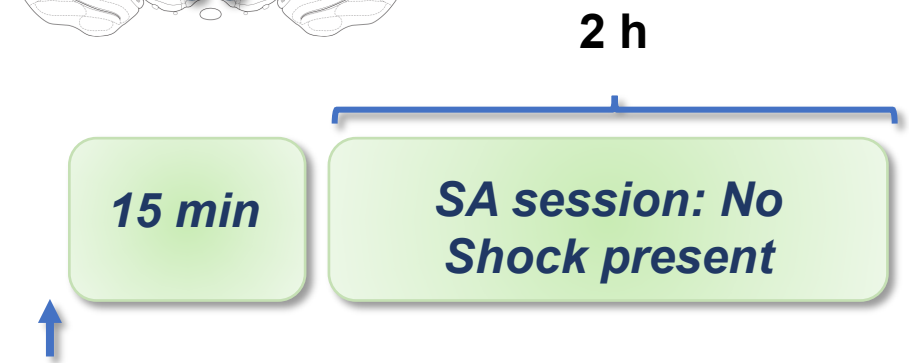
*p<.05, compared to No Shock; #p<.05, compared to Veh

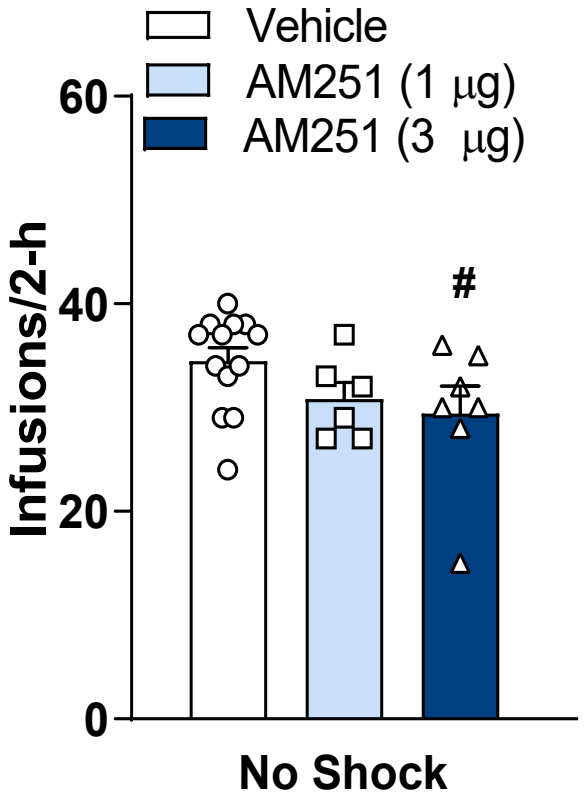
McReynolds et al, 2023 *NPP*

Intra-VTA administration of a CB1R antagonist attenuates cocaine SA

Acquisition → Stable Baseline responding → SA 2-h/day x 14 days → Remove stress component & test







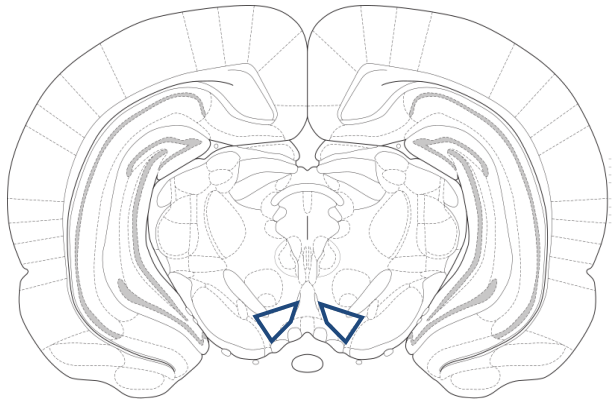
AM251 (0,1, or 3 µg/0.3 µL) – CB1R antagonist

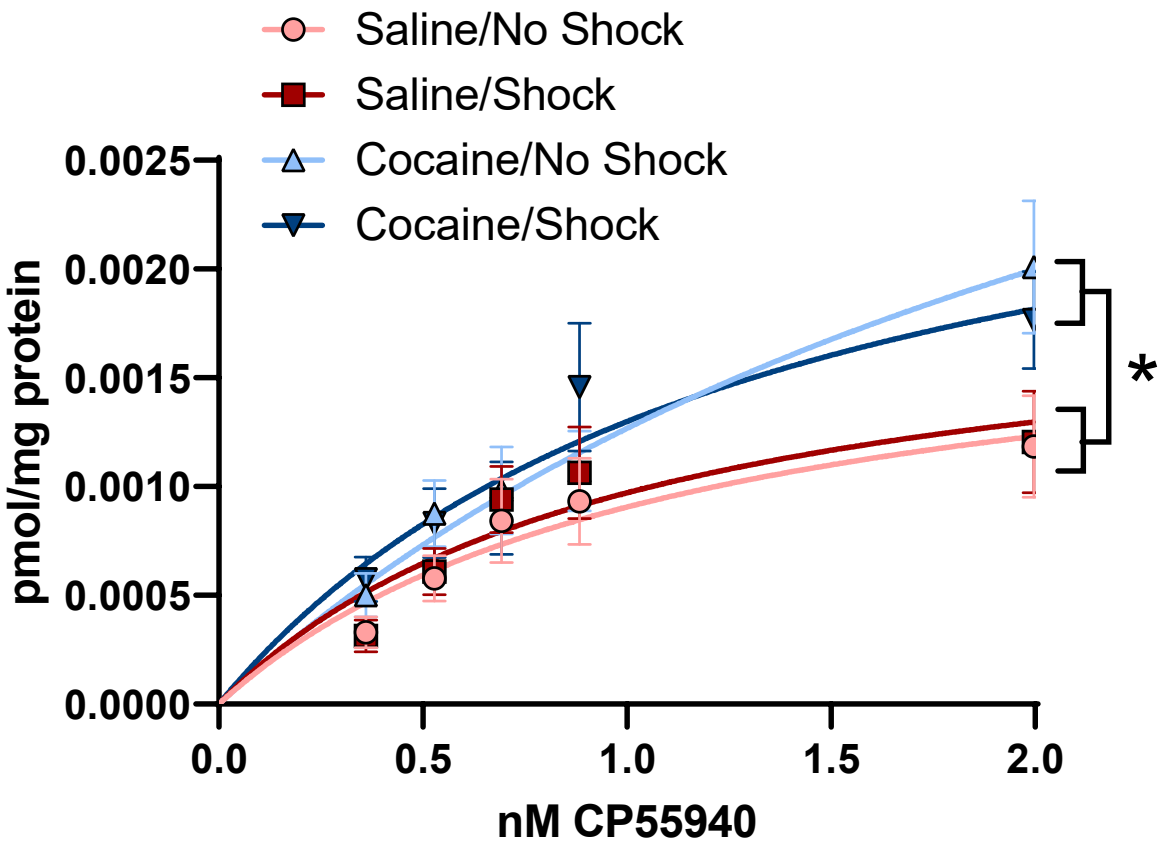
**p<.01, compared to No Shock; #p<.05, compared to Veh

McReynolds et al, 2023 *NPP*

Cocaine self-administration with or without stress increases CB1R density in the VTA

Acquisition → Stable Baseline responding → SA 2-h/day x 14 days → Collect brains 24 hr after SA14



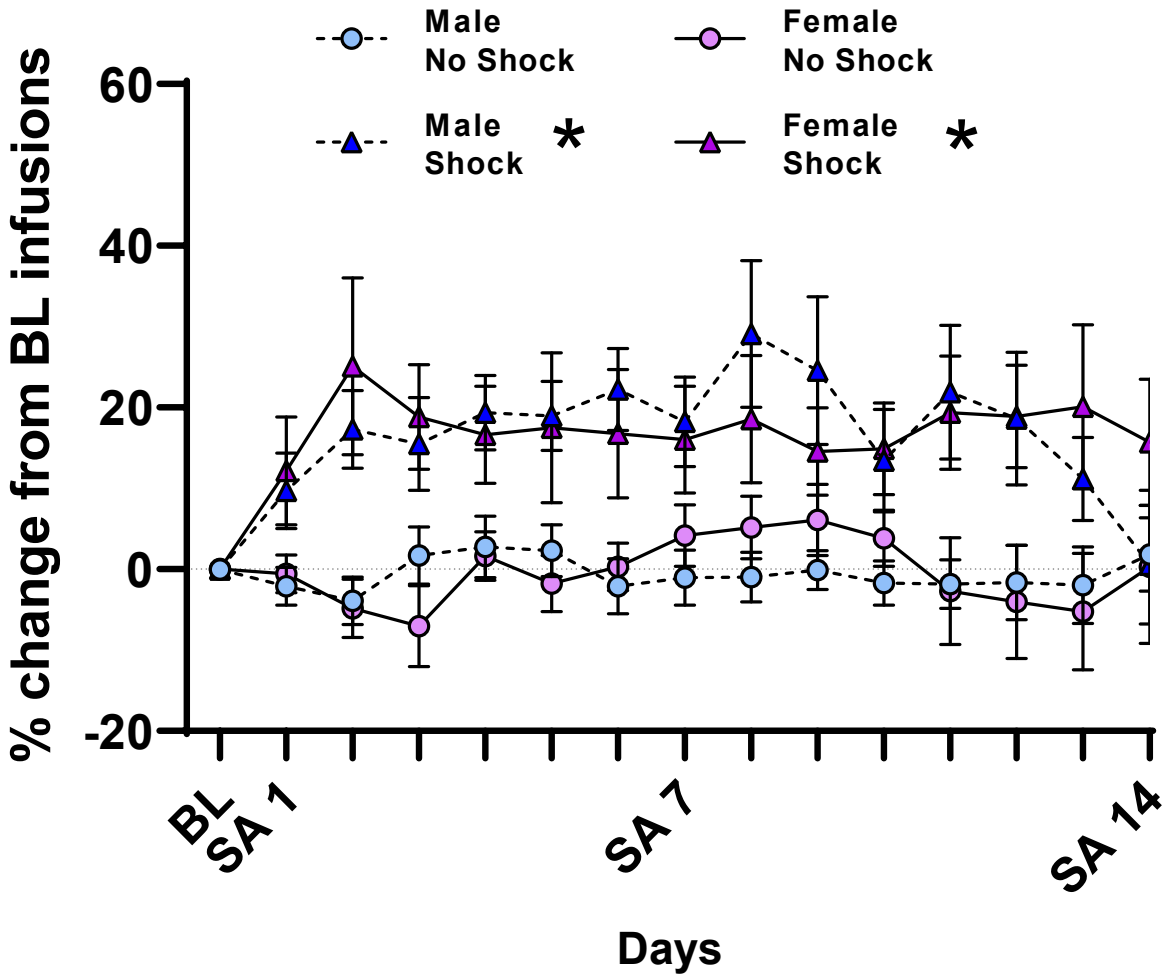


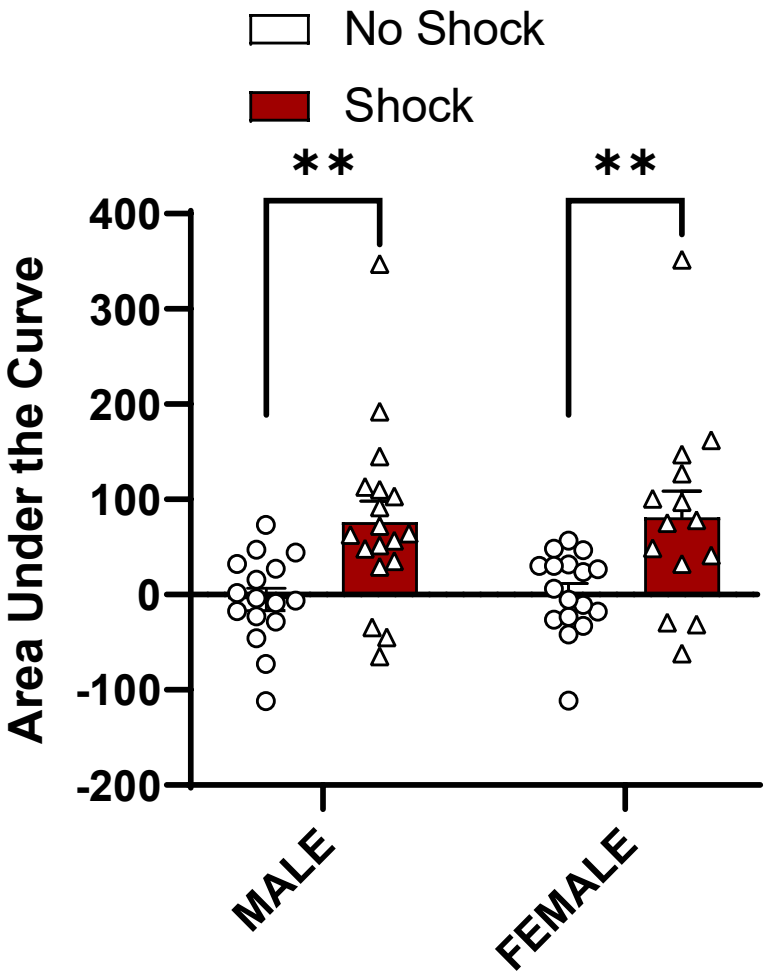
**p<.01, compared to Saline SA

McReynolds et al, 2023 *NPP*

What about females?

Stress-enhanced cocaine SA is observed in both male and female rats

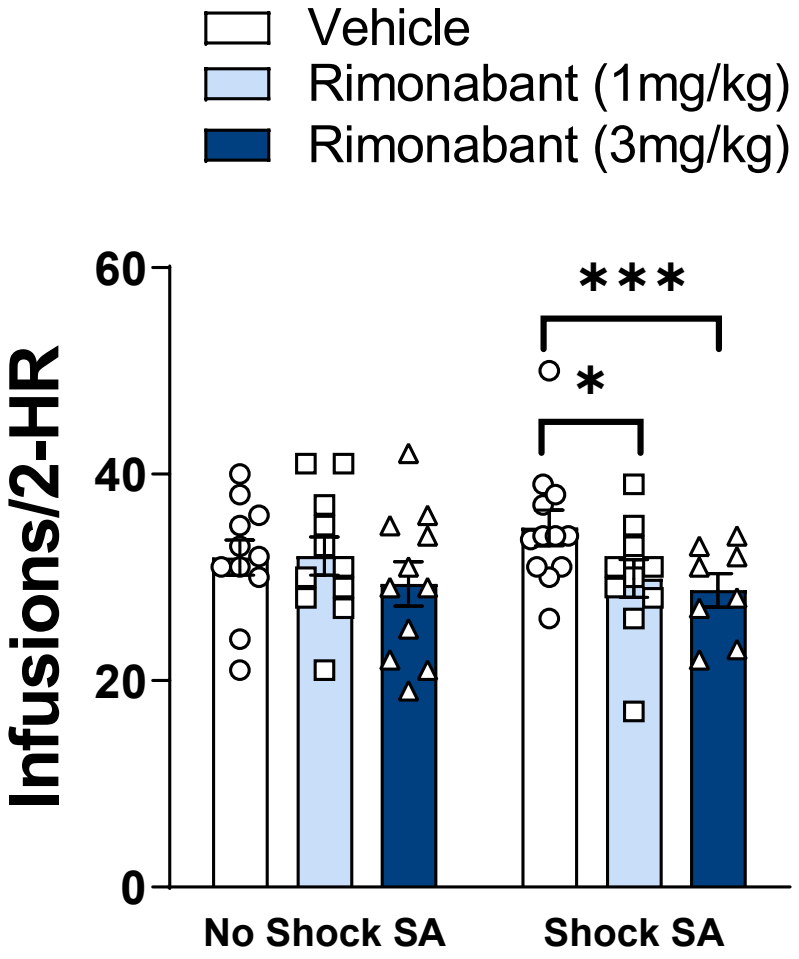


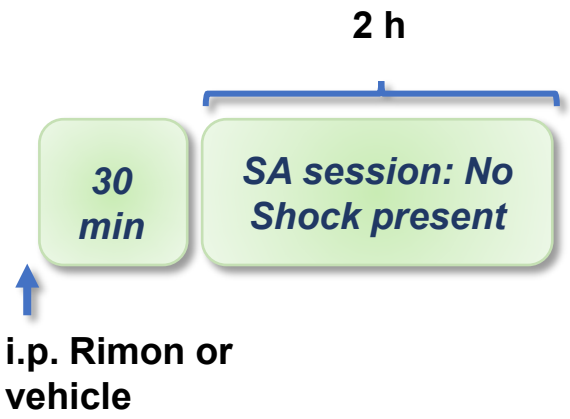


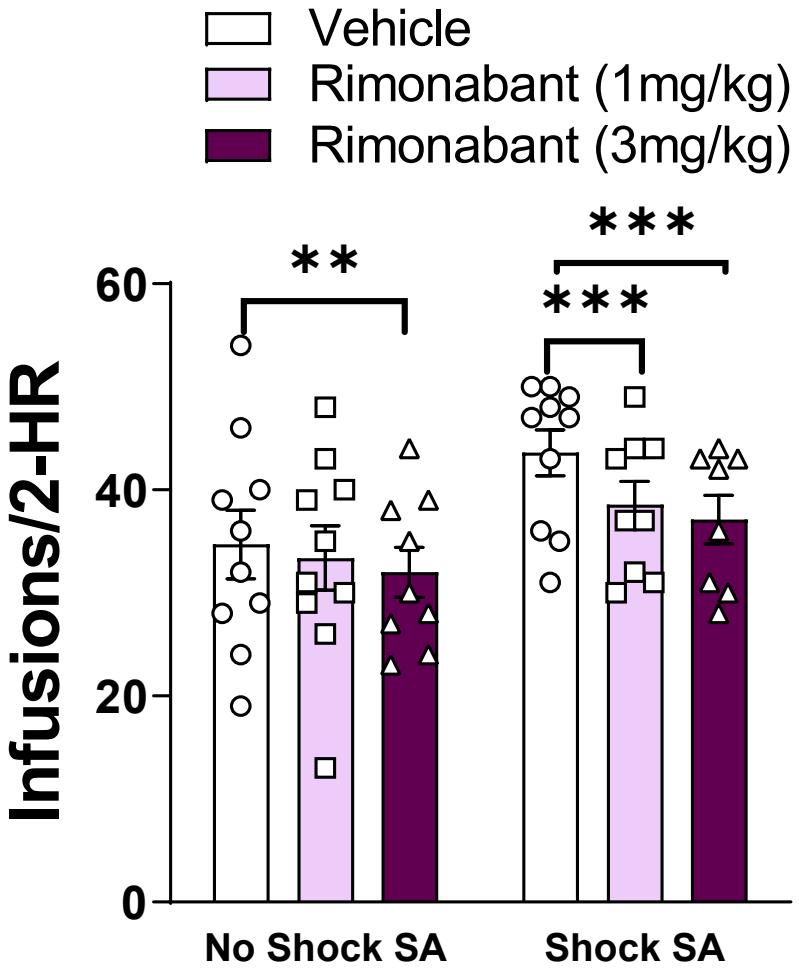
Andrew Gaulden

Gaulden et al, 2025 *Physiol & Behav*

CB1R antagonism attenuates cocaine SA in rats with a history of stress in male and female rats







Gaulden et al, 2025 *Physiol & Behav*

Are there inherent sex differences in how endocannabinoid signaling regulates cocaine-evoked dopamine?

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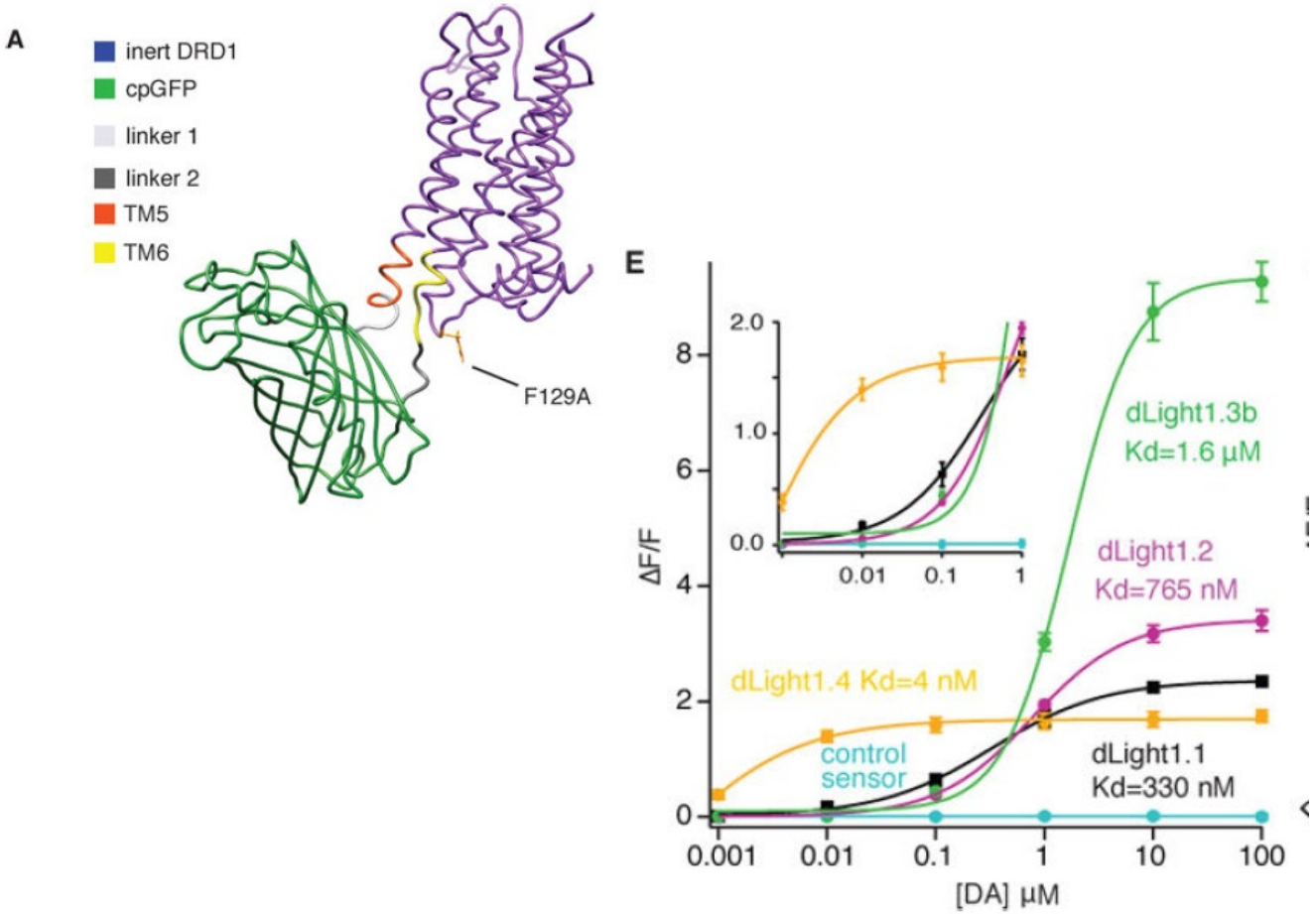
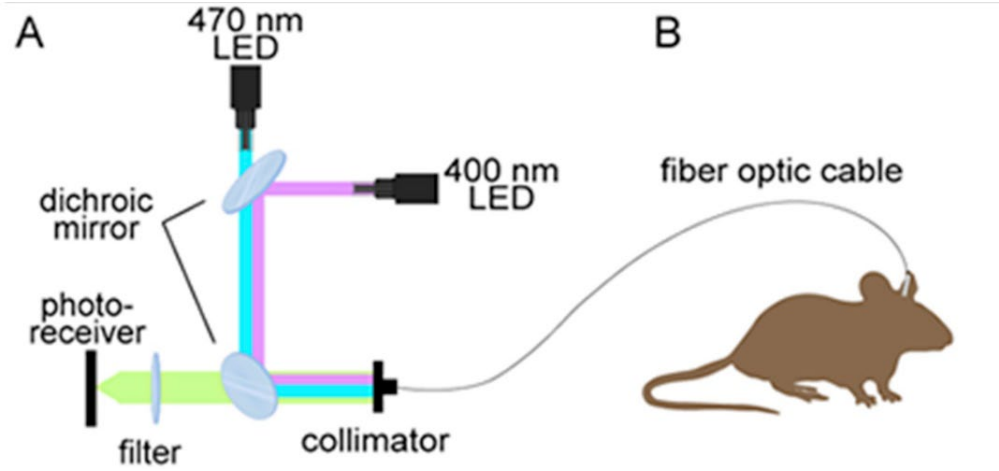
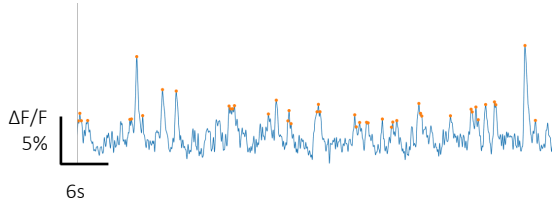
Measure *in vivo* changes in dopamine using new dopamine biosensors



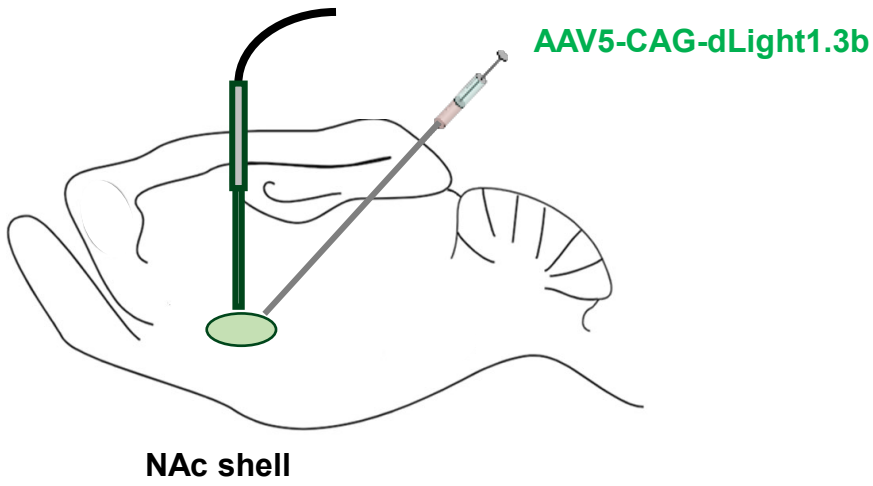
Patriarchi et al, 2018 *Science*

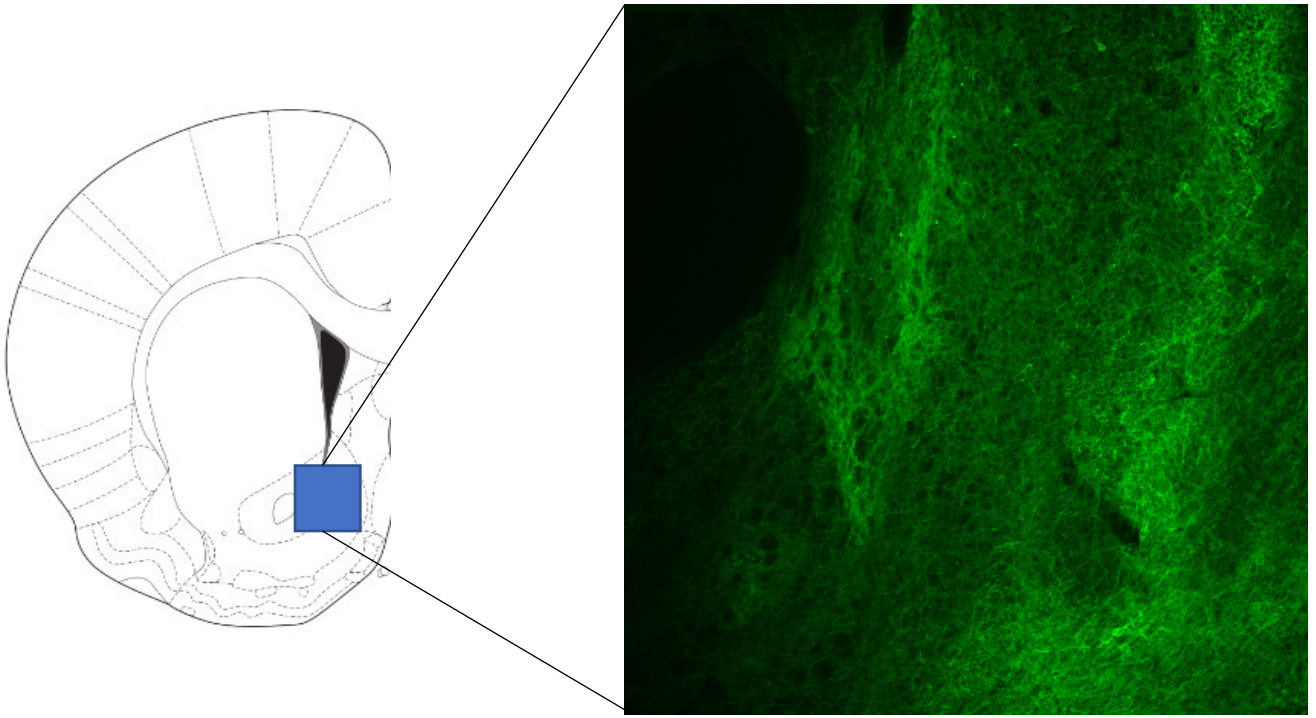


Siciliano & Tye, 2019 *Alcohol*



dLight expression in the nucleus accumbens shell





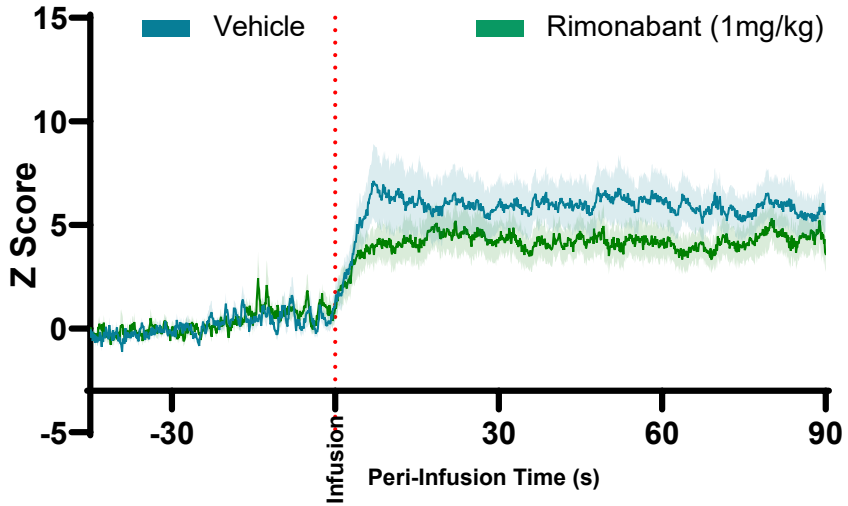
Females show increased sensitivity to CB1R regulation of cocaine-evoked NAc shell dopamine

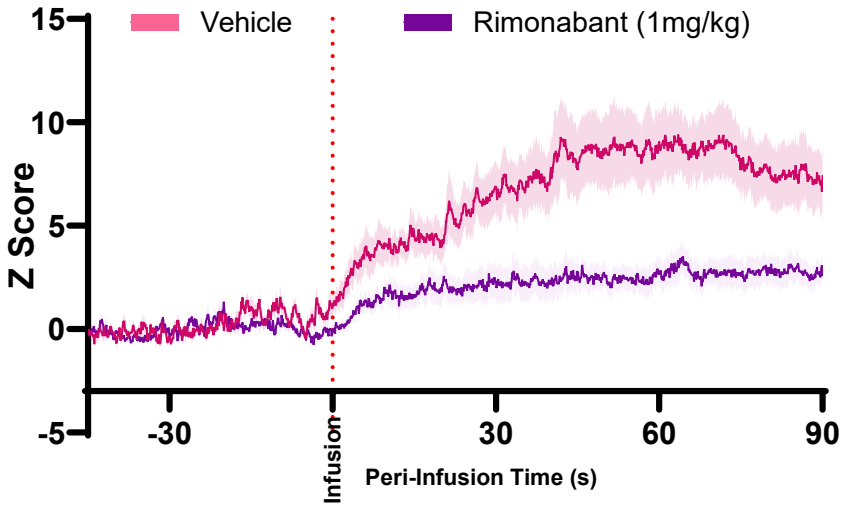
Andrew Gaulden

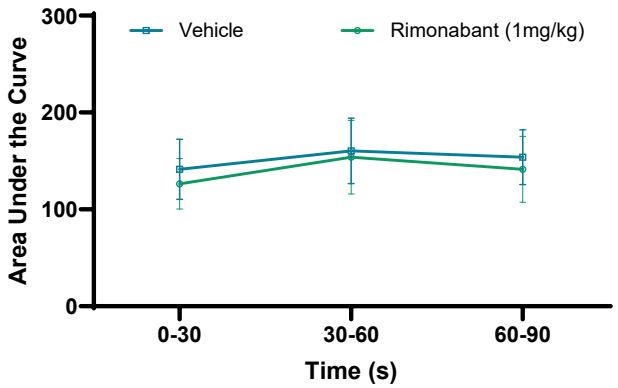
Male

i.p. injection (Veh or Rim) → 30 min → i.v. infusion (Sal or Coc)

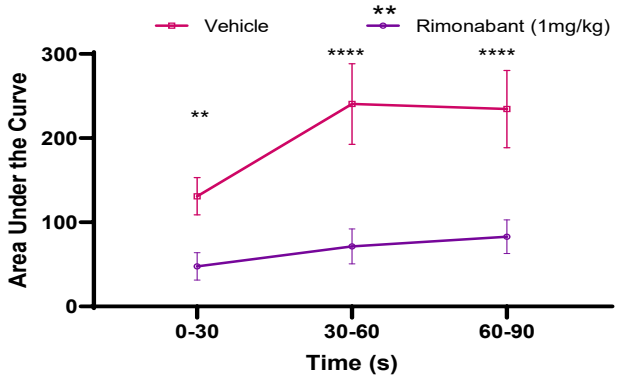
Female







Cocaine (3 mg/kg, iv)



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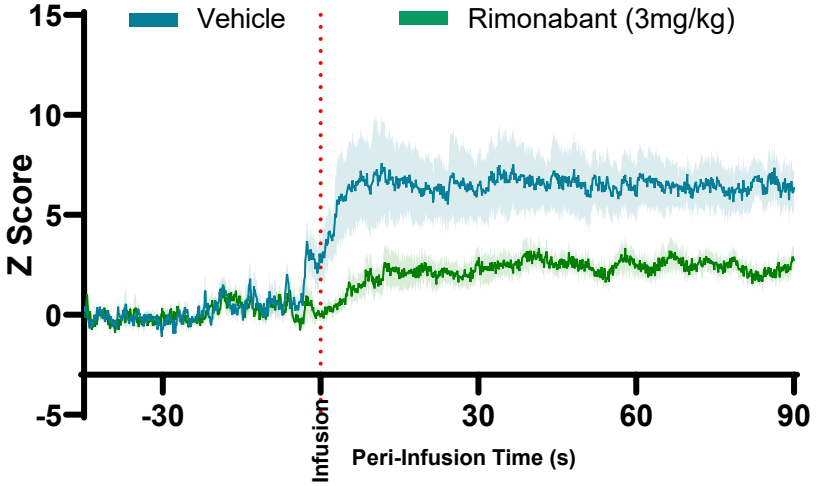
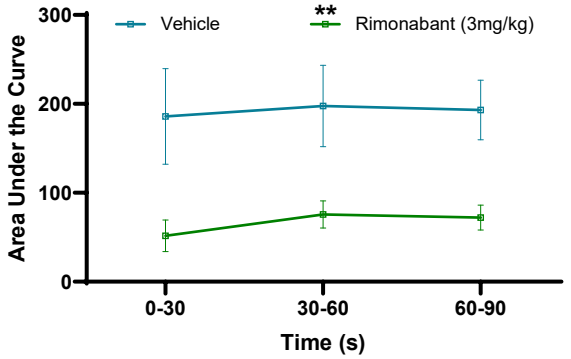
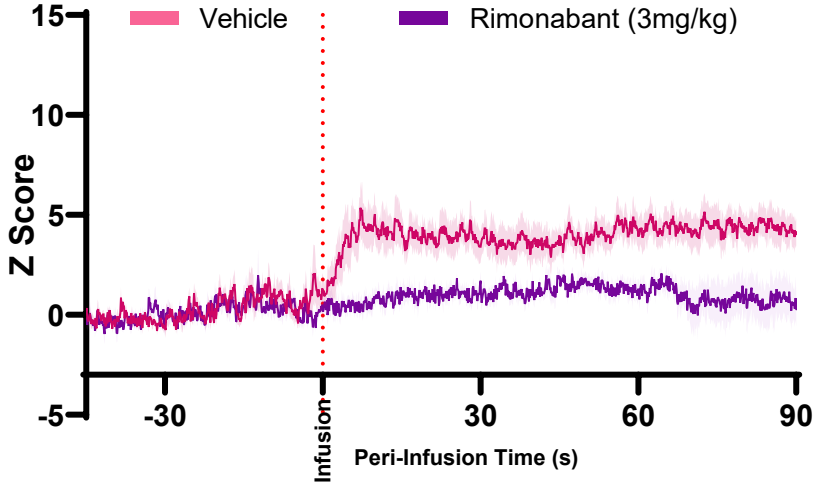
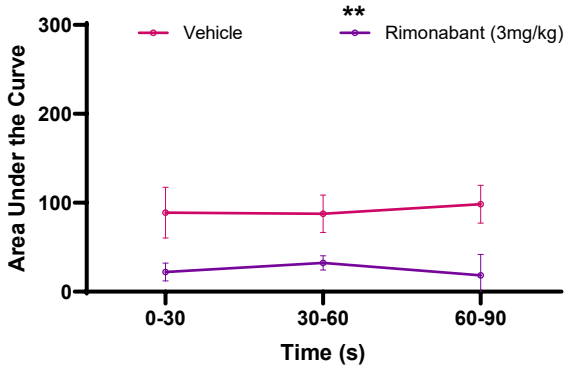




Female



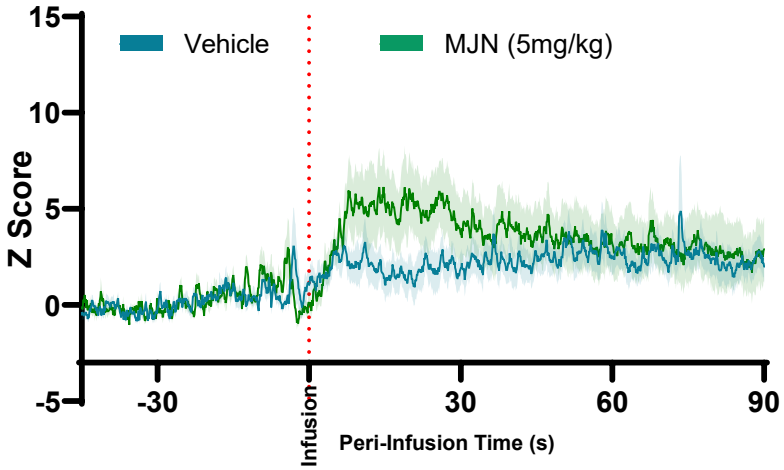


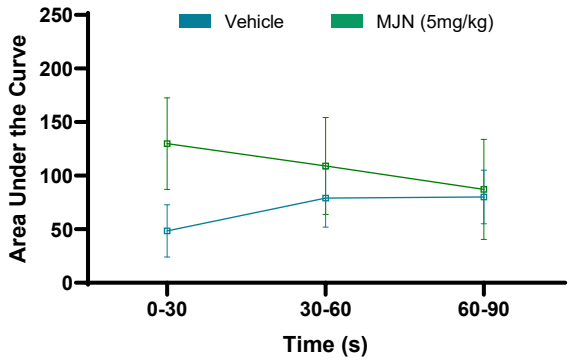
Cocaine (3 mg/kg, iv)

Elevating 2-AG levels enhances cocaine-evoked NAc shell dopamine

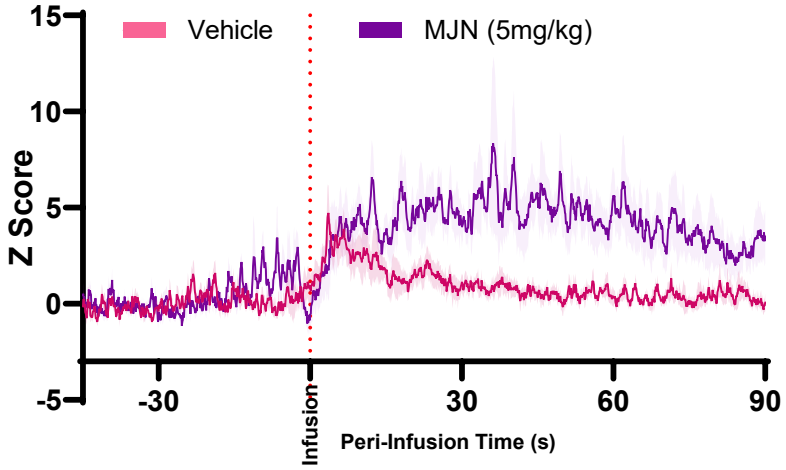
Andrew Gaulden

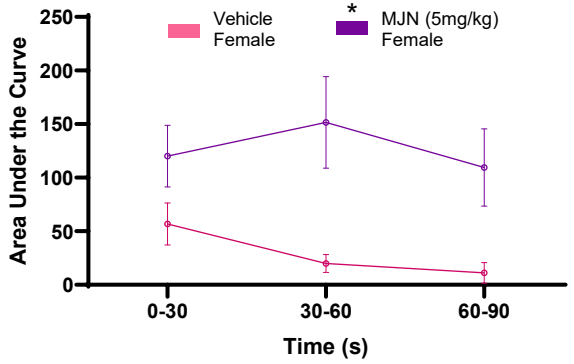
Male





Female





Cocaine (0.5 mg/kg, iv)

Is endocannabinoid signaling involved in stress-enhanced cocaine-seeking behavior?

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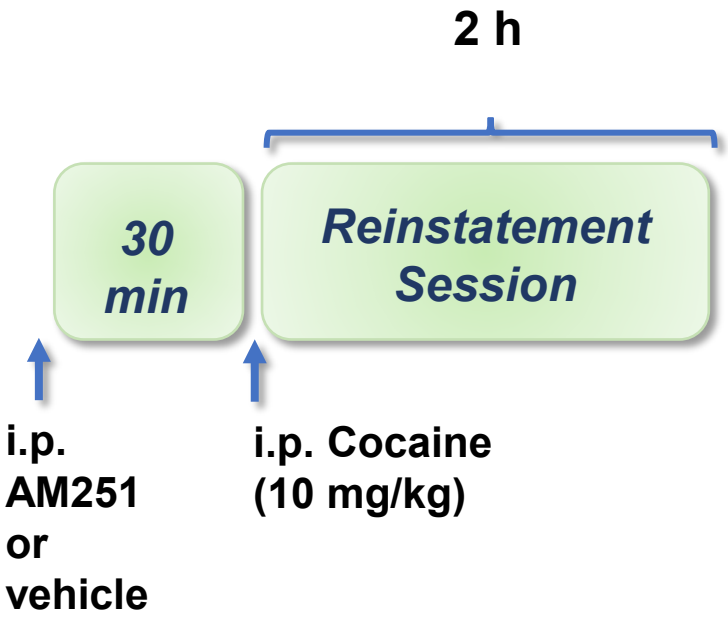
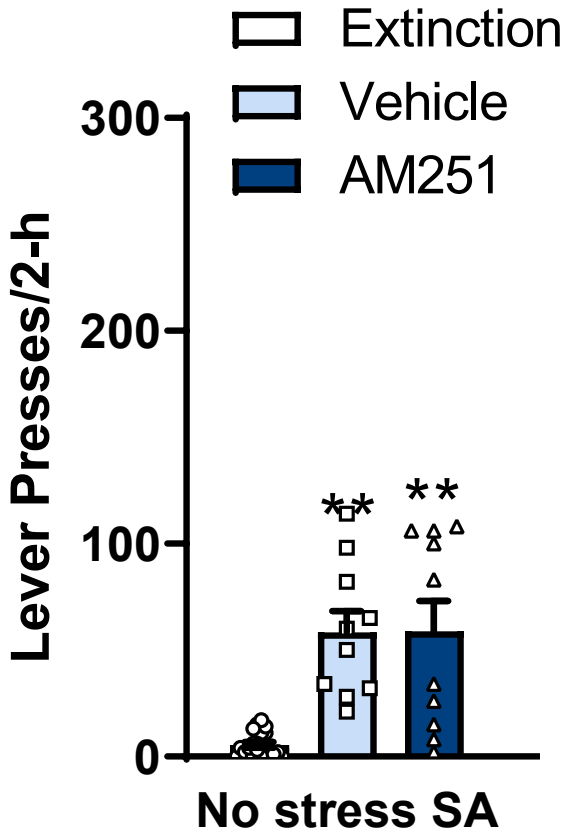
CB1R antagonism blocks augmented cocaine seeking only in rats with a history of stress



AM251 (1 mg/kg, i.p.) – CB1R antagonist

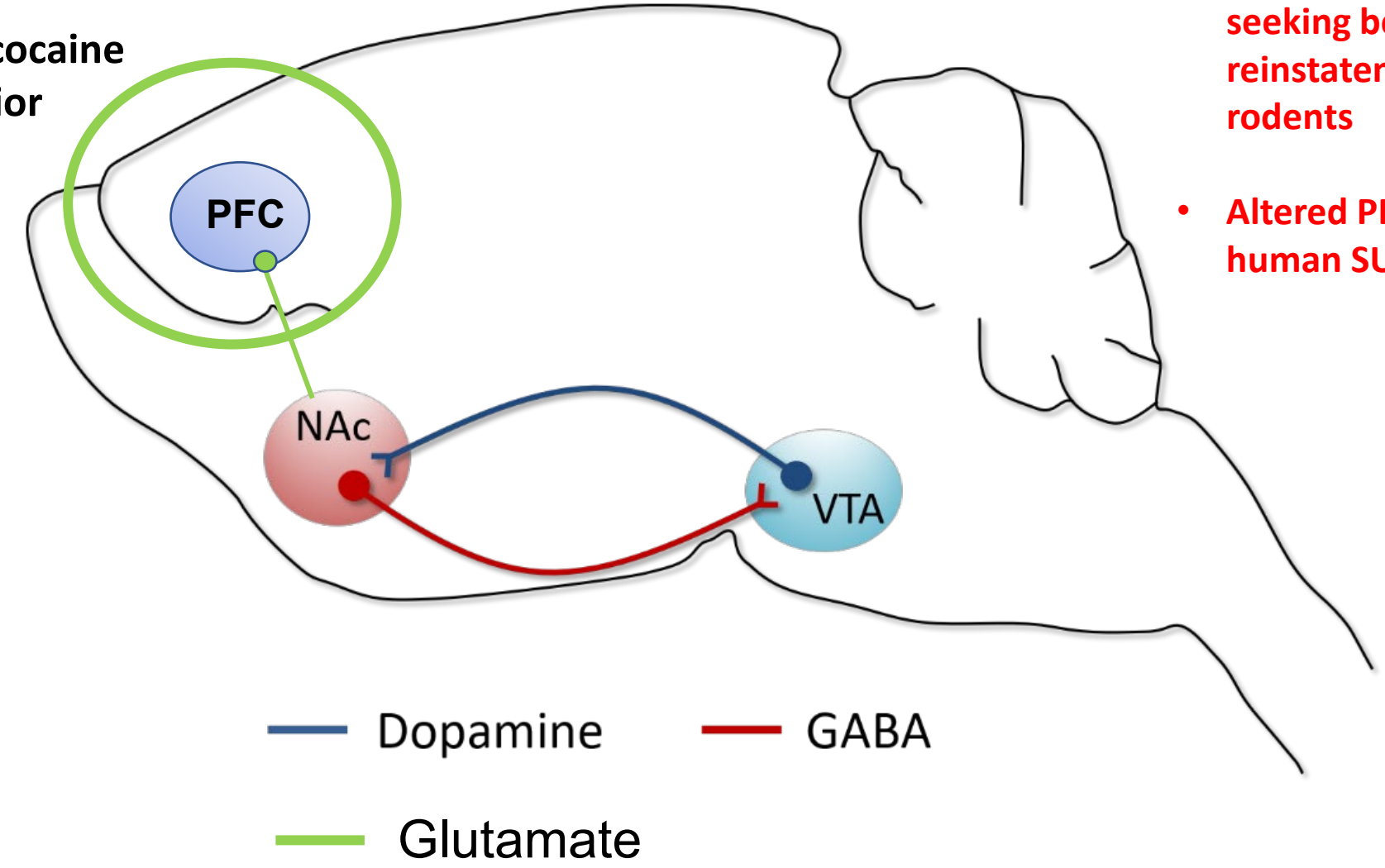


##p<.01, compared to Veh; **p<.01, compared to EXT; @p<.05, compared to No Shock

McReynolds et al, 2023 *NPP*

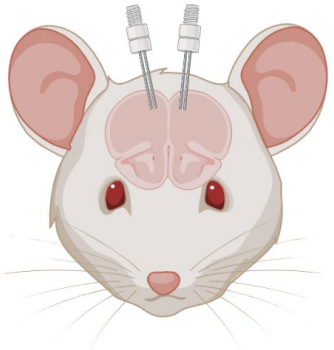
Regulation of endocannabinoids in regions critical for drug-seeking behavior

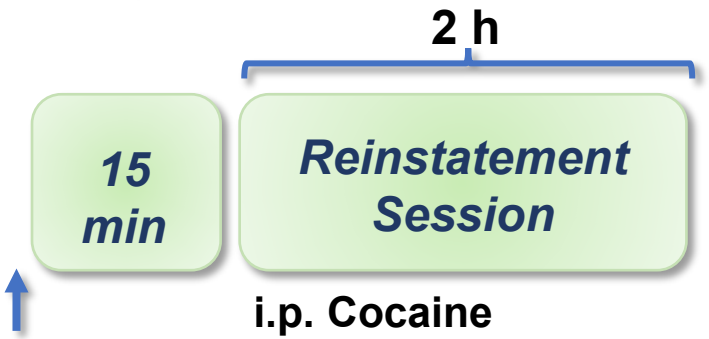
Regulation of cocaine seeking behavior

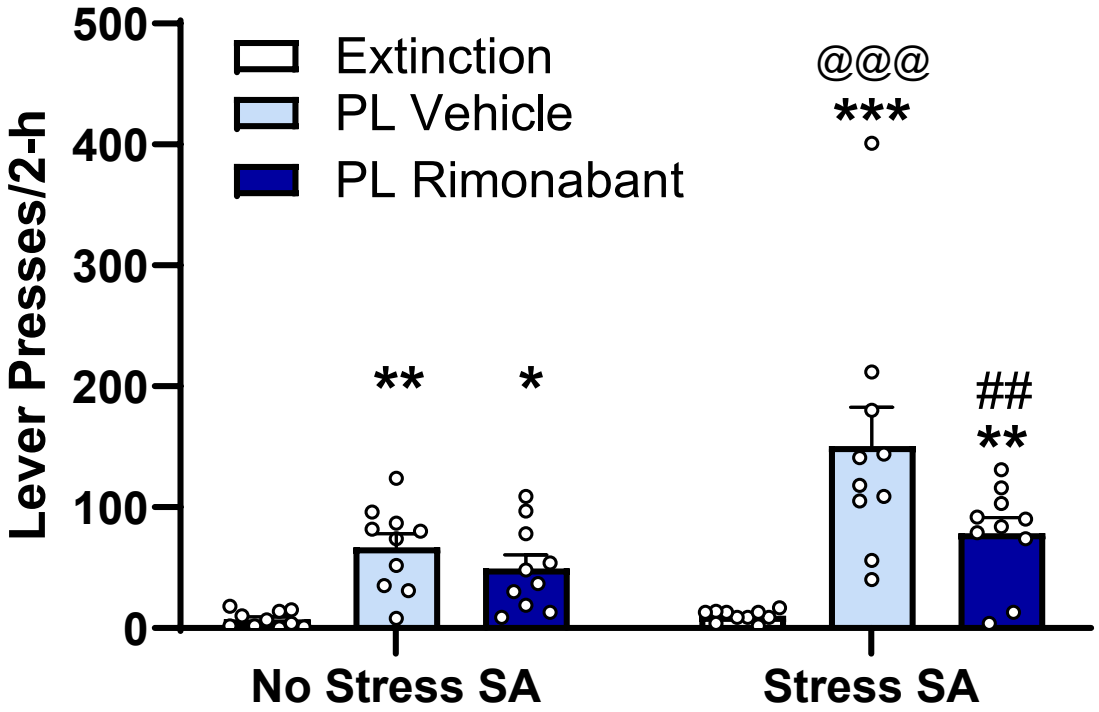


- **mPFC is critical for drug-seeking behavior across reinstatement stimuli in rodents**
- **Altered PFC activity in human SUD patients**

PrL CB1Rs are necessary for enhanced cocaine-seeking behavior following stress-induced enhancement of cocaine SA







Andrew Gaulden

Conclusions

- Chronic stress induces a glucocorticoid-dependent enhancement of cocaine self-administration that is the result of persistent neuroadaptations.

- These neuroadaptations likely result in changes in the endocannabinoid system as we see either selective or greater involvement of endocannabinoid signaling in rats with a history of stress.

- The endocannabinoid system is recruited by repeated stress in regions that are involved in drug-taking and drug-seeking behavior to drive drug self-administration and increase susceptibility to later reinstatement.

Conclusions

- Females appear to show increased sensitivity to endocannabinoid regulation of cocaine-related behavior
  - Females may show more benefit from endocannabinoid manipulation than males, even under non-stress conditions

- Taken together, these data suggest that endocannabinoid signaling may represent an interesting therapeutic target for the treatment of CUD, particularly for those in whom stress is a contributing factor
  - Elevated circulating levels of the endocannabinoid 2-AG in dependent cocaine users

- Understanding the unique mechanisms underlying the influence of stress on drug use, and its long-lasting consequences, has implications for identifying SUD subpopulations in whom stress is a predominant contributing factor and could allow for greater individualized treatment.

Acknowledgements

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NIH National Institute on Drug Abuse

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Q&A

Please unmute to ask a question OR type your question in the chat box.

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Thank you for joining us!

- Please take a few moments to complete the survey form. Scan the QR code below or use the survey link provided in the chat box, both will be emailed.
- The form is **required** to complete if requesting Ohio CE credit for Psychology.

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Psychedelics as Therapeutics for Substances Use Disorder: A Perspective on Their Neurobiology and Future Clinical Applications

- Wednesday, August 13, 2025: 12:00 – 1:00 PM
- Dr. Davide Amato and Mr. Jon Kostas

[Registration website: med.uc.edu/institutes/CAR/summer-speaker-series/speaker-series-2025](med.uc.edu/institutes/CAR/summer-speaker-series/speaker-series-2025)

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