Activity Of Prefrontal Cortex Subpopulations During Operant Alcohol Self-Administration

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INTRODUCTION

- The prefrontal cortex (PFC) plays an important role in decision-making, response inhibition, and drug-seeking.
- The PFC has been implicated in persistent drug self-administration despite negative consequences. However, the specific circuitry involved in inhibiting this behavior is unknown. Understanding the circuitry that mediates the "stop" signal may help us understand and treat compulsive alcohol drinking.
- Two candidate circuits are known to mediate 'stop responding' behavior in appetitive cognitive tasks: PFC projections to the dorsomedial striatum (PFC->DMS), and PFC projections to the medial mediodorsal thalamus (PFC->mMDT).[1]
- Learning more about these circuits could lead to future therapies for Alcohol Use Disorder, Substance Use Disorders, and compulsive behaviors.

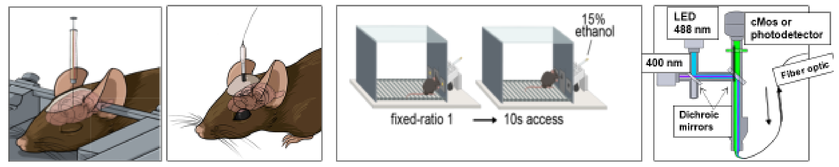
BACKGROUND

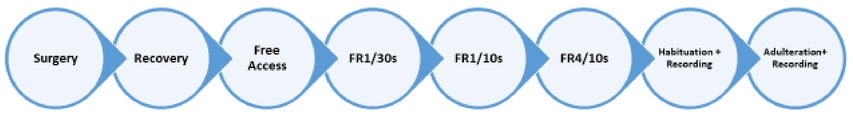
- Operant sipper models, wherein a mouse gains access to a sipper bottle of alcohol after a nosepoke, can be used to model alcohol reinforcement.[2]
- Mice that continue to drink despite the alcohol's adulteration with quinine, a bitter tasting substance, model compulsive-like drinking.[2]
- Genetically encoded calcium indicators (GECIs) allow proxy measurement of neuronal activity at a circuit level *in vivo* through fiber photometry.[3]

HYPOTHESIS

- We hypothesize that PFC neurons that project to the MDT and DMS will show relatively increased fluorescent activity in mice that withhold their responding versus mice that show compulsive-like alcohol responding.
- We predict atomoxetine (Strattera), an inhibitor of the presynaptic norepinephrine transporter, would increase activity in these cell populations and decrease drinking.

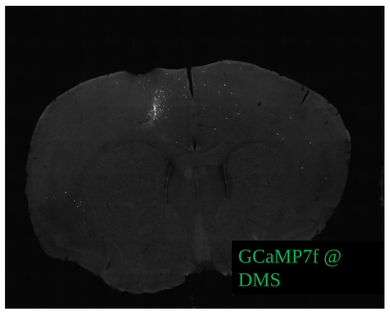
METHODS

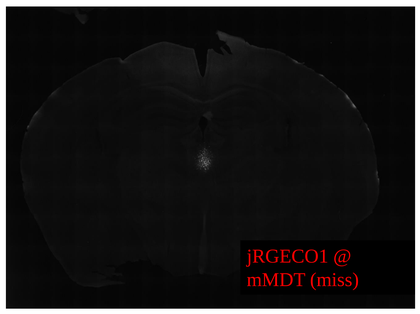




Surgeries

- Adult male and female C57BL/6J mice were injected with retrograde AAVs in order to express the GECIs GCaMP7f (green) in the DMS or jRGECO1 (red) in mMDT, or vice versa.



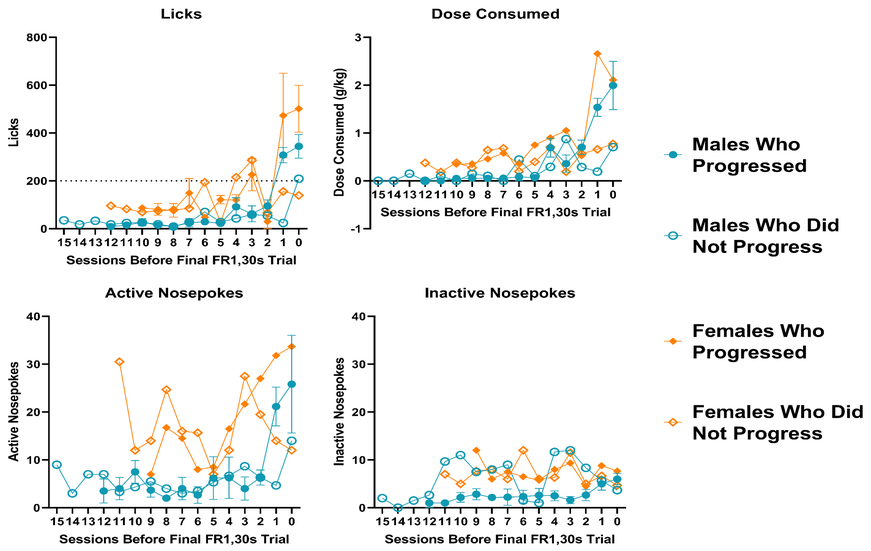


Training

Training Schedule	
Program	Graduation Criteria
Home Drinking	3 days of alcohol graduation to 15%
2 Hour Free Access Box Drinking	3 days of drinking minimum and 2 consecutive days of >200 licks
2 Hour FR1, 30s Access	2 days of >200 licks
2 Hour FR1, 10s Access	2 days of >200 licks
2 Hour FR4, 10s Access	Habituation with tether
2 Hour FR4, 10s Access with Quinine Adulteration	

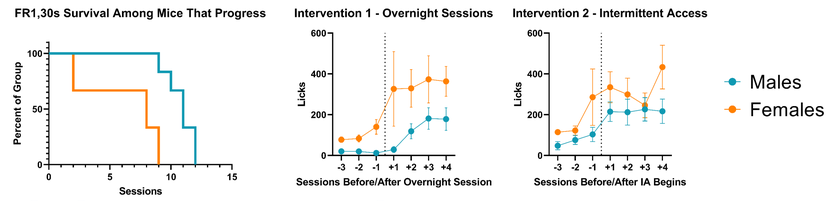
RESULTS

Progressions Over FR1,30s Sessions



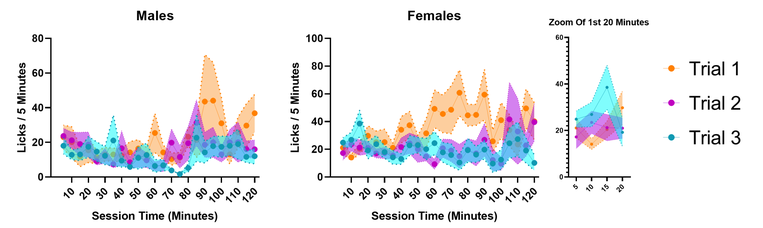
Training Challenges

- Two interventions were used to improve drinking.

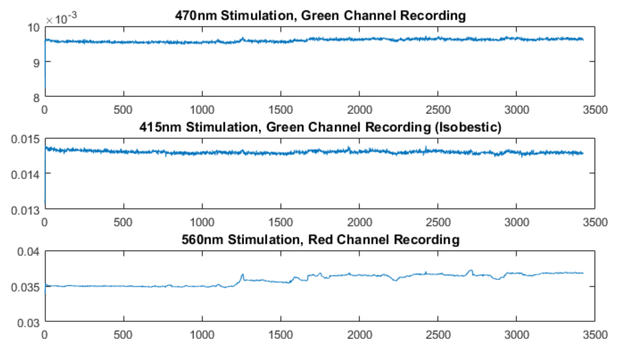


Lick Typography

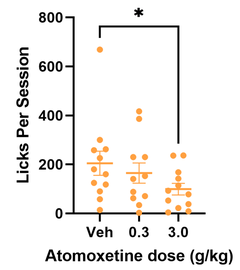
First 3 Free Access Sessions



Fiber Photometry Recording



Atomoxetine Dose On Licks



CONCLUSIONS

- Atomoxetine administration (3mg/kg i.p.) reduced alcohol consumption. We are now studying atomoxetine's motor effects.
- Overnight sessions and intermittent access improved mouse training.
- The laboratory is being trained on fiber photometry analysis to determine whether early recordings show signal.
- Quinine adulteration will begin when fiber photometry signals are verified.

References: [1]de Kloet et al., 2021. [2]Blegen et al., 2018, *Alcohol*, [3]Siciliano and Tye, 2019, *Alcohol*

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