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"Activity Of Prefrontal Cortex Subpopulations During Operant Alcohol Self-Administration"

The National Institute of Alcohol Abuse and Alcoholism states, 'according to the 2019 [National Survey on Drug Use and Health], 14.5 million (nearly 15 million) people ages 12 and older[1] (5.3 percent of this age group[2]) had [alcohol use disorder (AUD)].' The DSM-5 criteria for AUD includes compulsive drinking behavior.[3] The prefrontal cortex (PFC) has roles in decision-making, response inhibition, and drug seeking and likely plays a role in compulsive alcohol drinking. However, the specific circuitry involved is unknown. There are two PFC circuits implicated in response inhibition or 'stop' behavior: PFC projections to the dorsomedial striatum (DMS) and PFC projections to the medial mediodorsal thalamus (mMDT).[4]

This pilot study sets out to identify the two circuits' roles in mediating 'stop drinking' behavior. We hypothesize that PFC neurons that project to the MDT or DMS will show relatively increased fluorescent activity in mice that withhold their alcohol drinking versus mice that compulsively drink alcohol.

Genetically encoded calcium indicators (GECIs) allow proxy measurement of neuronal activity *in vivo* through fiber photometry.[5] Adult male and female C57/BL6J mice were injected with the GECIs AAV-rg-jRGECO1 in the DMS and AAV-rg-GCaMP7f in the mMDT, or vice versa, and implanted with a fiber optic cannula in the PFC. Following surgery, these mice were trained on an operant sipper paradigm for alcohol drinking with the goal of recording calcium activity from these PFC subpopulations using fiber photometry during drinking sessions before and after the alcohol's adulteration with quinine, a bitter additive.

Over twenty-two sessions, 95% of mice reached criterion for free access drinking. Males reached criterion to progress from FR1/30 second sipper access to FR1/10 second sipper access in a minimum of nine days, while females reached criterion in a minimum of two days. 45% of mice reached the final criterion, FR4/10 second access, qualifying them for recording. Mice showed improvement in progression through their training after one twelve-hour operant behavior session and switching from daily access to intermittent access. Preliminary fiber photometry recordings suggest presence of a calcium signal.

This schedule, with the addition of twelve-hour sessions and intermittent access appears to induce heavy drinking in adult male and female mice. In our ongoing experiments, we will continue to measure calcium activity during drinking sessions before and after quinine adulteration.

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[1] SAMHSA, Center for Behavioral Health Statistics and Quality. 2019 National Survey on Drug Use and Health.
[2] SAMHSA, Center for Behavioral Health Statistics and Quality. 2019 National Survey on Drug Use and Health.
[3] NIAAA, Fact Sheets, Alcohol's Effects On Health, *Alcohol Use Disorder: A Comparison Between DSM–IV and DSM-5.* Accessed July 22, 2022.
[4] de Kloet et al., 2021, *Nature Communications*
[5] Siciliano and Tye, 2019, *Alcohol*