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**“Evaluation of PFC-MdT circuit deletion on behavioral measures of cognition and alcohol consumption”**

Alcohol Use Disorder (AUD) is a medical condition that has harmful effects on individual health and society. AUD is characterized by an impaired cognitive ability to stop or control alcohol use despite its reoccurring negative consequences. Chronic alcohol consumption creates a dangerous negative feedback cycle by compromising brain structure, resulting in executive dysfunction, and increasing the likelihood of continued alcohol preference and consumption. The prefrontal cortex (PFC) structure and function is critically connected with the cognitive processes often disrupted by alcohol consumption. AUDs have a higher likelihood of developing in adolescence, especially when the age of onset is early adolescence because of alcohol's impact on underdeveloped PFC neural circuitry. One circuit the PFC is intimately in communication with is the mediodorsal thalamus (MdT) which regulates impulsivity and cognitive control. We have previously found that mice given voluntary access to alcohol during their adolescence have behavioral deficits consistent with local PFC and MdT lesions on the objection in place recognition task. However, there is a lack of causal understanding on how this circuit specifically affects these same behaviors and impacts alcohol consumption in adulthood. Therefore, we hypothesize that deletion of the PFC->MdT shows a similar behavioral profile to adolescent alcohol and that it increases alcohol consumption during adulthood.

We tested this hypothesis by deleting the PFC-> MdT circuit through retrograde-AAV techniques and Cre/Lox systems, so PFC to MdT projecting neurons expressed caspase-3 versus control (red-fluorescence-protein to green-fluorescence-protein reporter). Because executive dysfunction is associated with alcohol preference, we used a voluntary intermittent access to alcohol, with increasing dosages, and an every-other-day drinking model in adolescent male and female mice to investigate whether disrupted PFC to MdT connection brings about altered behavioral preference to alcohol. Our behavioral data yielded unexpected results, as we observed reduced performance in PFC->MdT caspase-3 mice on the novel object recognition task, but increased performance on object recognition task and Y-maze. In addition, we did not observe differences in alcohol consumption between groups following increasing alcohol concentration, but we did observe increased alcohol consumption and blood alcohol levels in control mice compared to PFC->MdT caspase-3 mice. We analyzed and confirmed the virus's targeting using imaging of control viral expression red fluorescent protein (virus transduction) and green fluorescent protein (Cre-recombination). Our data leads us to a better understanding of how PFC function via the PFC->MdT pathway is affected by circuit deletion strategy. Further study can work towards better understanding these cognitive pathways involved with alcohol so that these circuits can ultimately be enhanced as a form of treatment and recovery in cases of AUD.