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"Characterization of adolescent alcohol consumption in preclinical model of ADHD"

Background: Attention deficit hyperactivity disorder (ADHD) is a highly heritable neurodevelopmental disorder characterized by deficits in attention, hyperactivity and impulsivity. Previous studies have found that ADHD is a major risk factor for addictive behaviors, such as alcohol use disorder (AUD). Individuals with ADHD have been shown to initiate alcohol drinking earlier and more robustly in adolescence than their non-affected peers which also accelerates the development of an AUD. AUDs are also highly heritable and in fact ADHD and AUDs share several genetic risk factors including the variants in the *LPHN3* gene. *LPHN3* encodes a cell adhesion G-protein coupled receptor (GPCR) known as latrophillin-3 which has a prominent role in forming and maintaining glutamatergic synapses. Constitutive deletion of *Lphn3* in rats and mice leads to impulsivity, attentional deficits, and hyperactivity compared to their wildtype littermates and is considered a leading ADHD preclinical model. It is unknown how *Lphn3* deletion affects alcohol consumption during adolescence. Gaining insight into LPHN3's role in neurological functioning could lead to a greater understanding in the relationship between ADHD and AUD.

Methods: To obtain a pan-neuronal knockout of *Lphn3*, we crossed synapsin-Cre mice with floxed *Lphn3* mice. Wildtype, heterozygous, and mutant conditional KO male and female mice were the given access to alcohol during adolescence (PND30 to 60) using an intermittent 2-bottle choice method. We additionally used RNASCOPE to determine that Lphn3 transcription was reduced in neurons compared to wildtype littermates. We collected plasma to determine blood alcohol levels reached during drinking days.

Results: We found that Lphn3 KO and Het mice did not show any changes in daily alcohol consumption during adolescence. Blood alcohol levels were not statistically different amongst the genotypes. Curiously, when we delete Lphn3 specifically in the prefrontal cortex using a viral strategy, we observe an escalation in alcohol consumption and increased blood alcohol levels in KO mice.

Conclusion: Our pan-neuronal deletion of *Lphn3* leads to observable differences in behavior consistent with an ADHD phenotype, for instance increased locomotor activity and increased novelty seeking behaviors, however alcohol consumption during adolescence was not affected. Our proof of principle, RNAscope data supports that we are effectively deleting *Lphn3* expression in neurons with the pan-neuronal strategy. Further work focused on why PFC dependent deletion of Lphn3 increases alcohol consumption and pan-neuronal deletion does not will be explored, but we suspect that full deletion of a gene may cause an additional, nonspecific effects on behavior that interfere with alcohol consumption.