



Dysregulation of *SLC1A3* in AUD and alcohol-associated behaviors

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Alcohol use is a large public health problem

➤ Alcohol Global Impact

- Alcohol use contributes to ~5% of the global burden of disease and injury (2.4 million deaths annually).

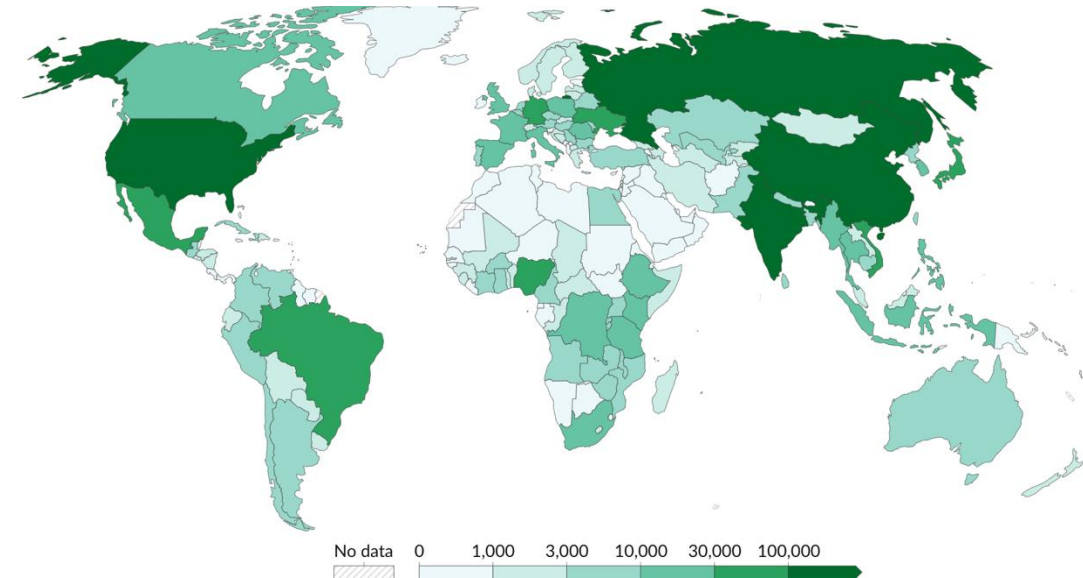
➤ Alcohol Use Disorder (AUD) is a significant contributor to alcohol-related burden, affecting ~11% of the US population (NIAAA)

➤ AUD is characterized by:

- Loss of control over alcohol intake
- Drinking continues despite negative consequences (“compulsivity”)
- Preference of alcohol over natural rewards

➤ DSM-5 focuses on behavioral patterns over the quantity of alcohol consumption.

- These behavioral symptoms reflect persistent neuroadaptations in key brain structures that control motivated behavior

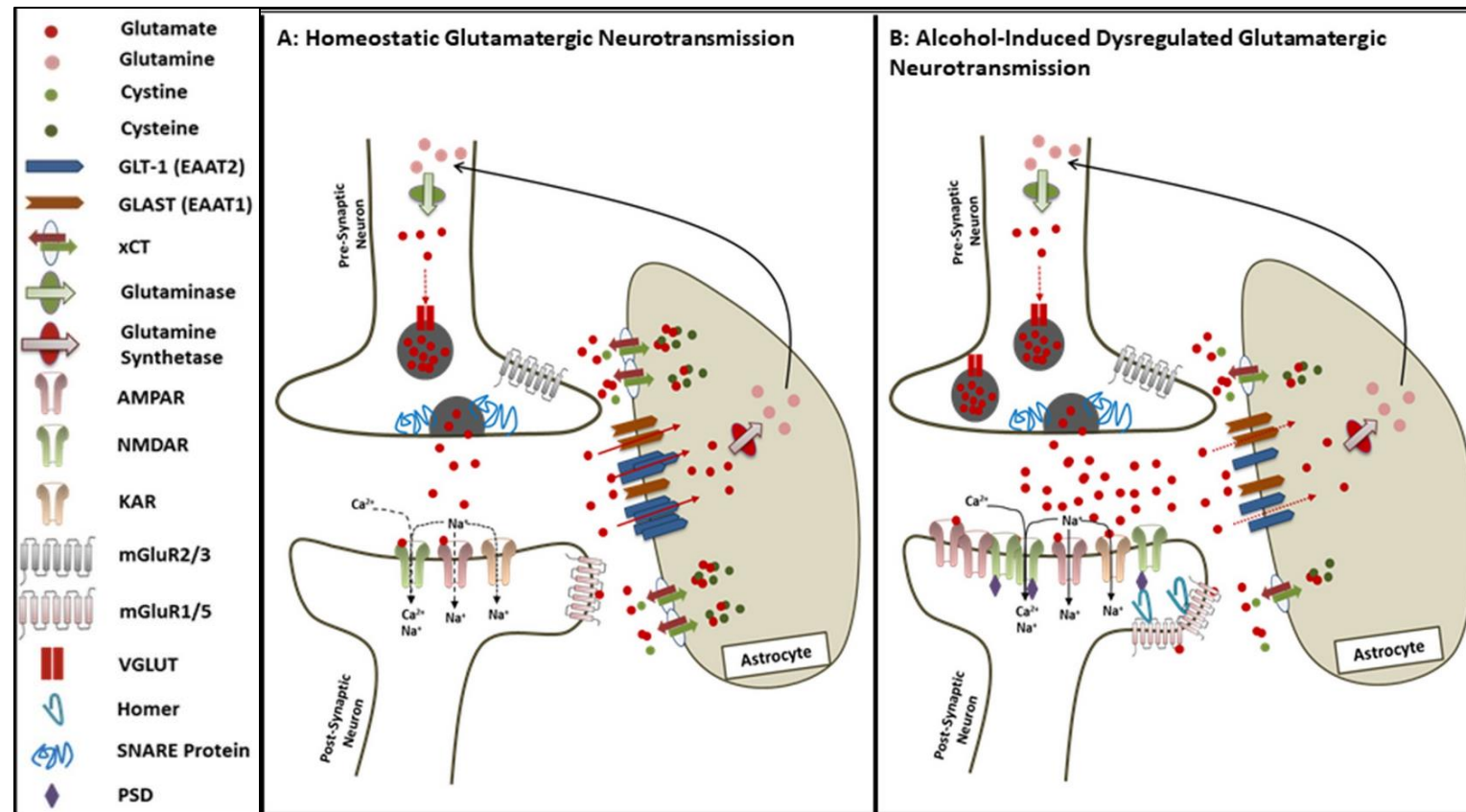


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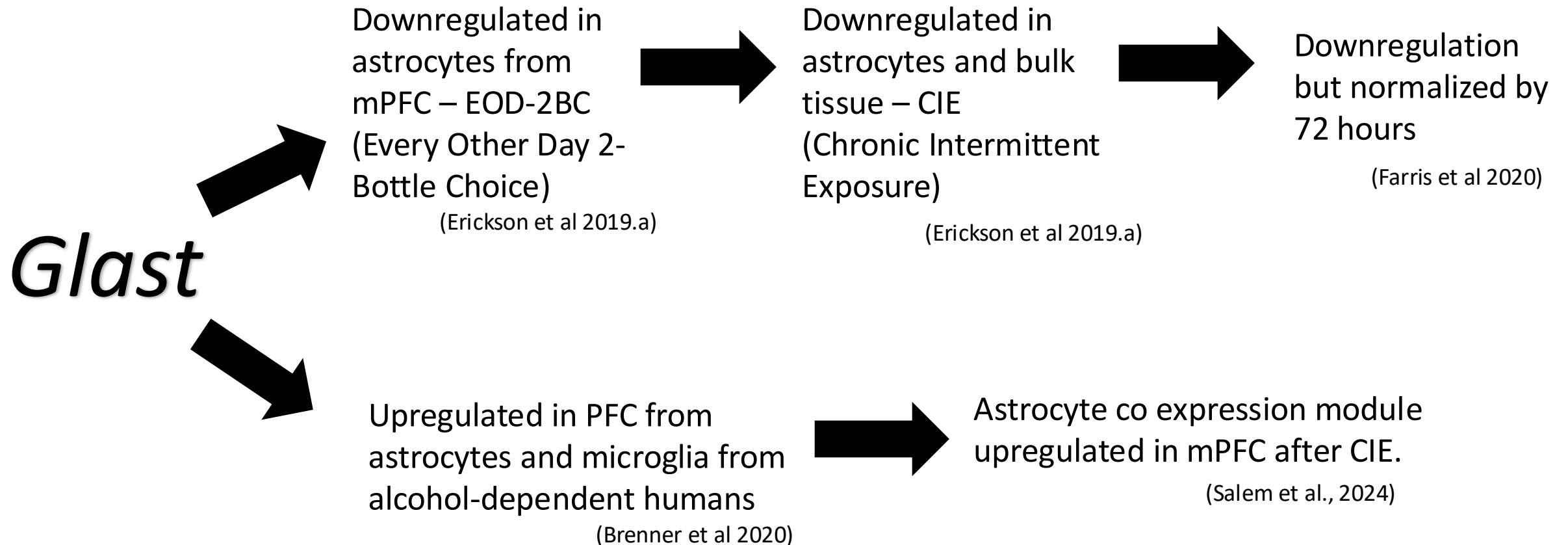
Alcohol disrupts glutamate homeostasis – ‘via GLT-1 downregulation’

- Primary Glu transporters are SLC1A2 and SLC1A3 (*Glast*)
 - SLC1A2 is more abundant (~1% of total brain protein)
 - *Glast* is 4-6 times less abundant than SLC1A2
- Extracellular Glu reuptake by SLC1A2/SLC1A3
 - Chronic alcohol exposure and withdrawal lead to elevated levels of extracellular glutamate
- GLT-1 (SLC1A2):
 - Cocaine, opioids, ethanol, nicotine, and amphetamines have each been shown to affect GLT-1 expression and glutamate uptake; mainly in the nucleus accumbens and prefrontal cortex

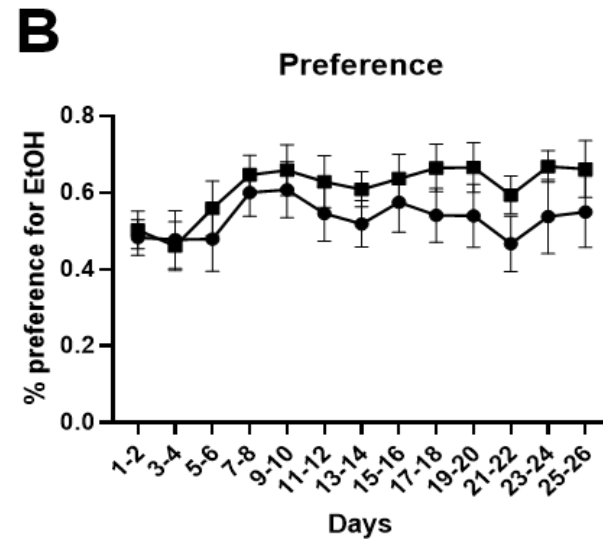
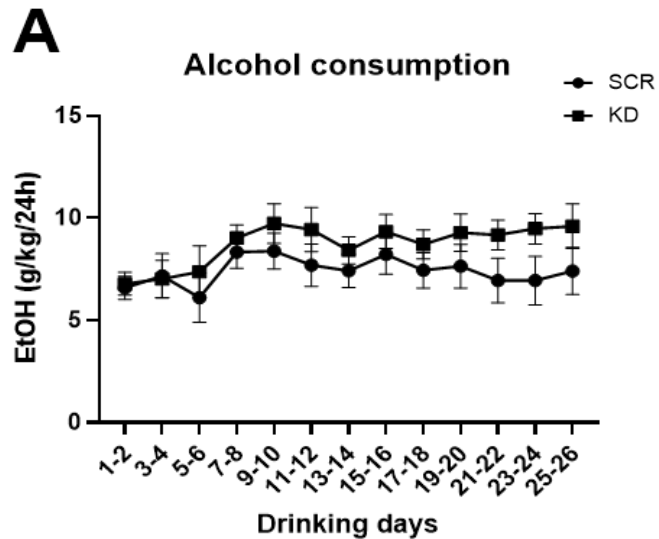
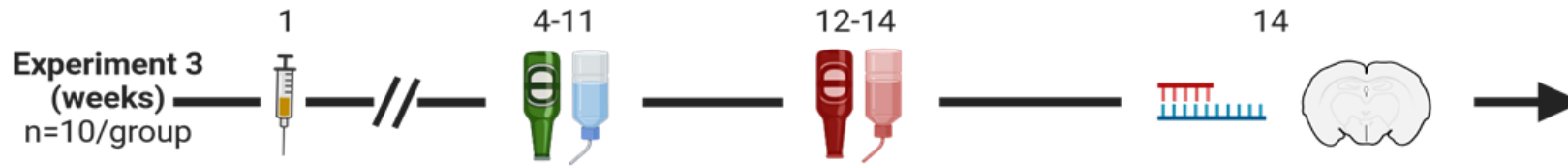
Reviews: Alasmari *et al.*, 2018; Roberts-Wolfe & Kalivas 2015



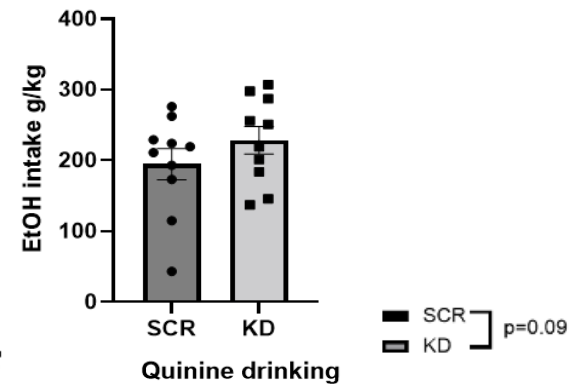
In our experiments, *Glast* is frequently found dysregulated



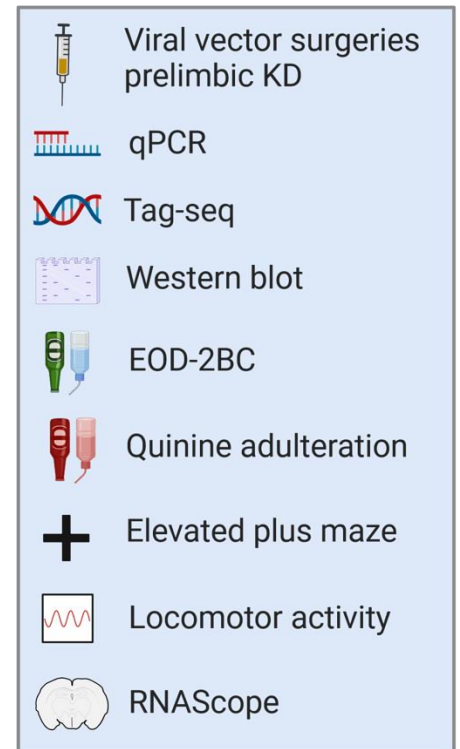
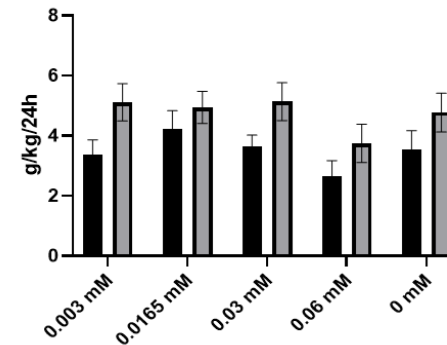
Glast KD in the dmPFC resulted in a small but stable increase in alcohol consumption in mice



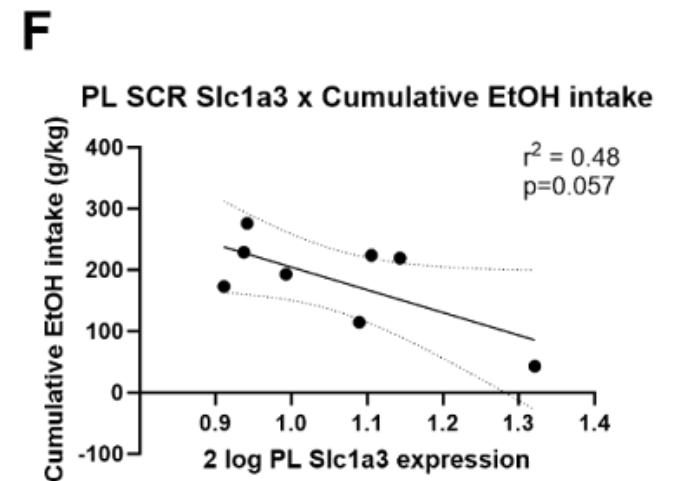
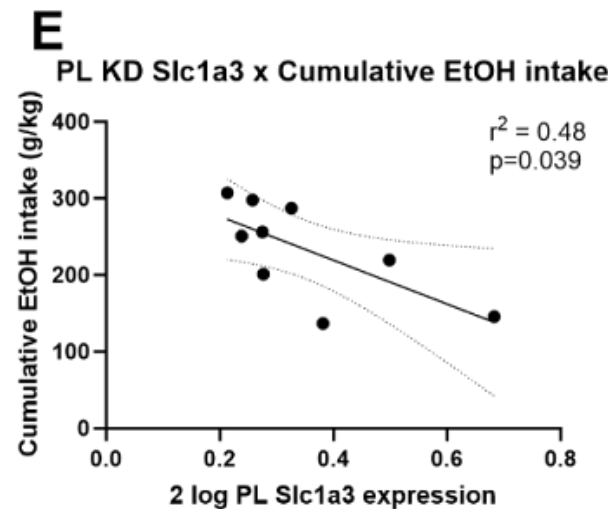
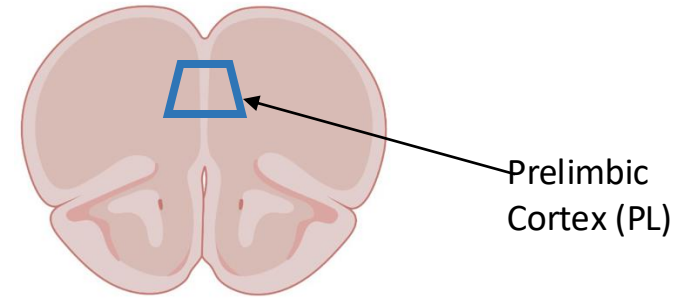
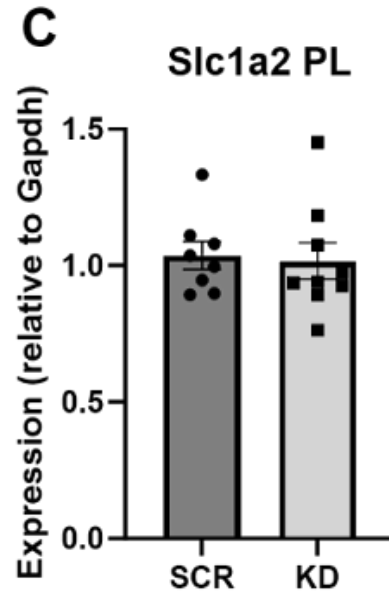
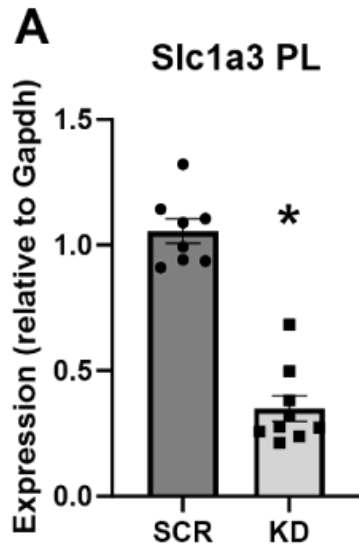
D Cumulative EtOH intake



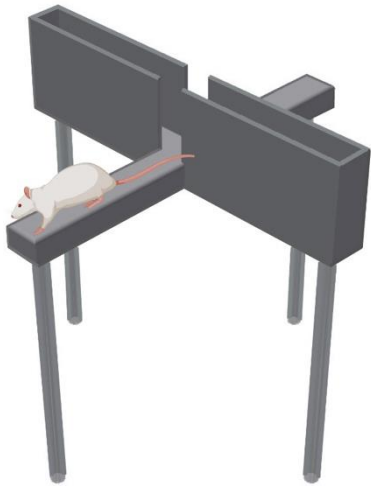
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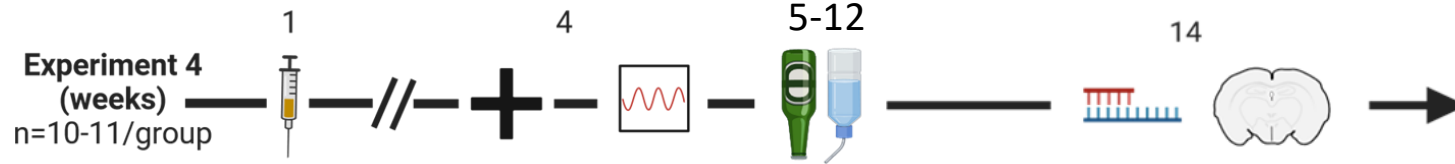
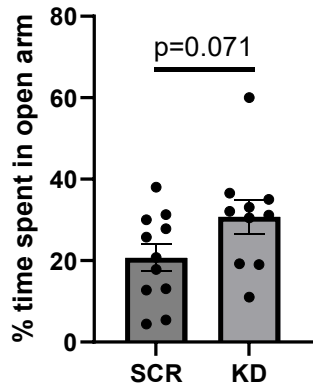
Expression levels of prelimbic *Glast* inversely correlated with cumulative voluntary EtOH intake



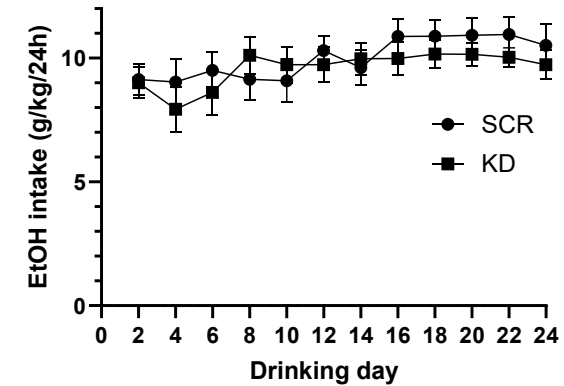
In a separate experiment, KD of *Glast* in the dmPFC showed no effect



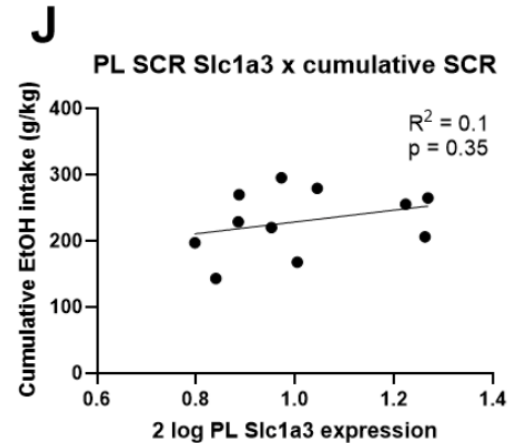
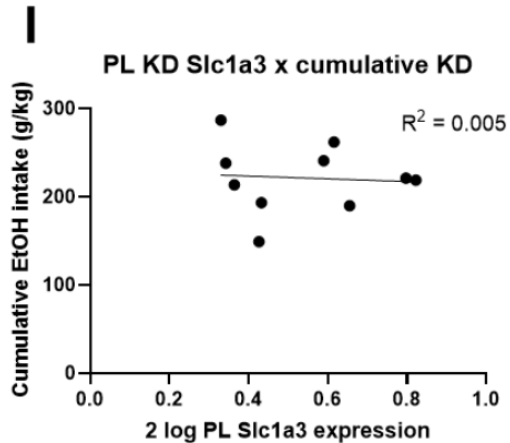
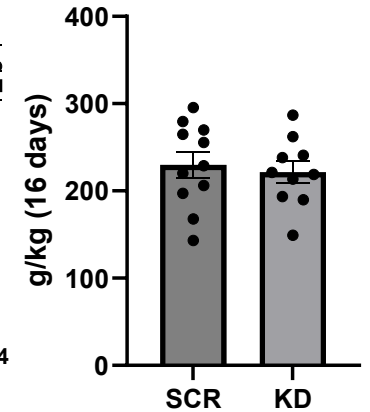
Elevated plus maze



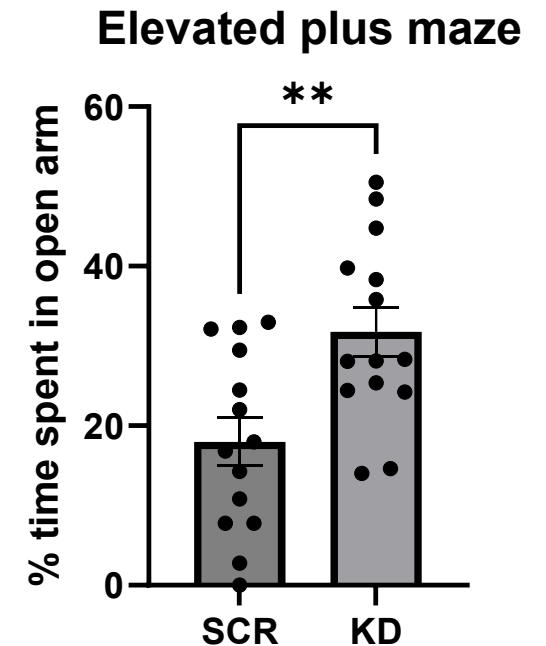
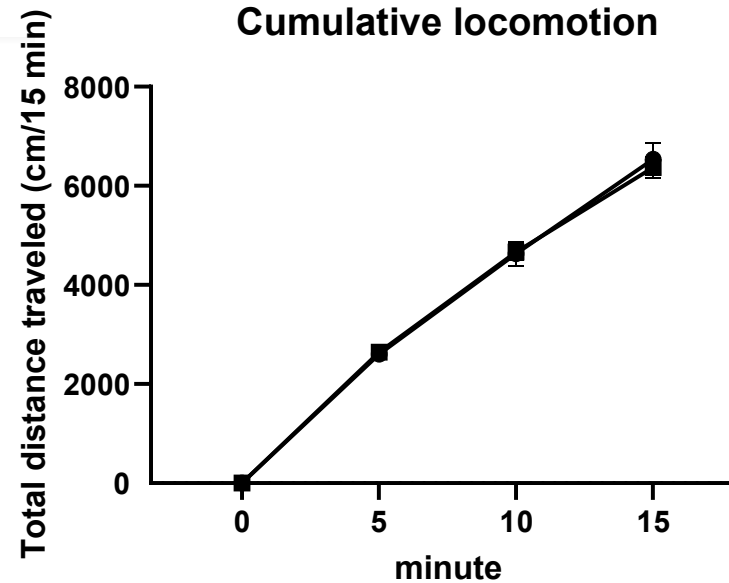
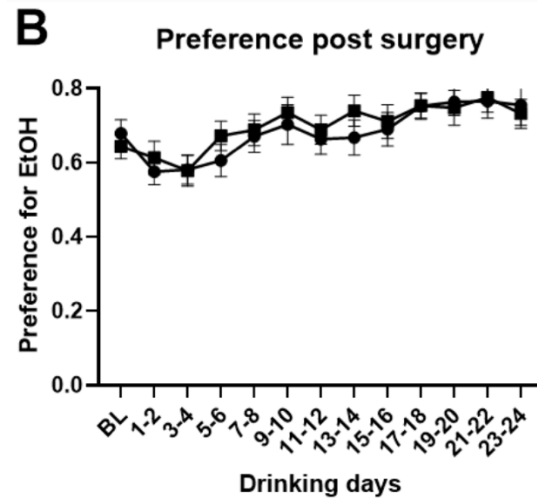
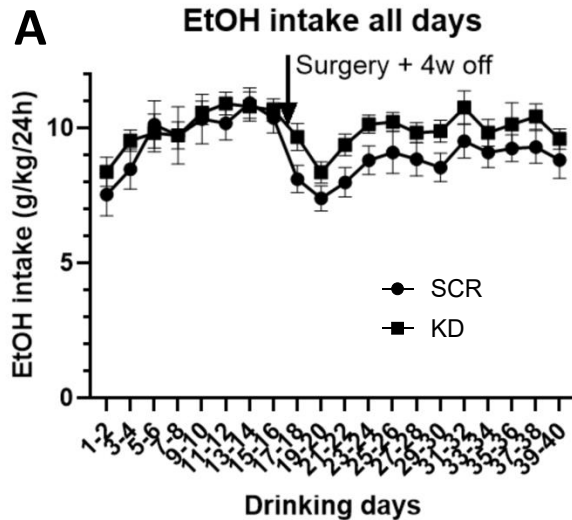
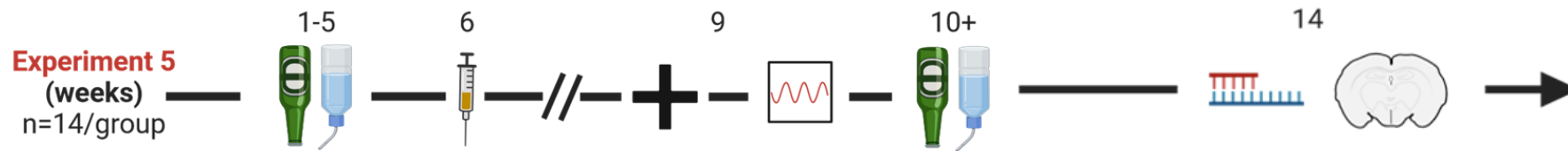
Alcohol consumption



Cumulative EtOH intake



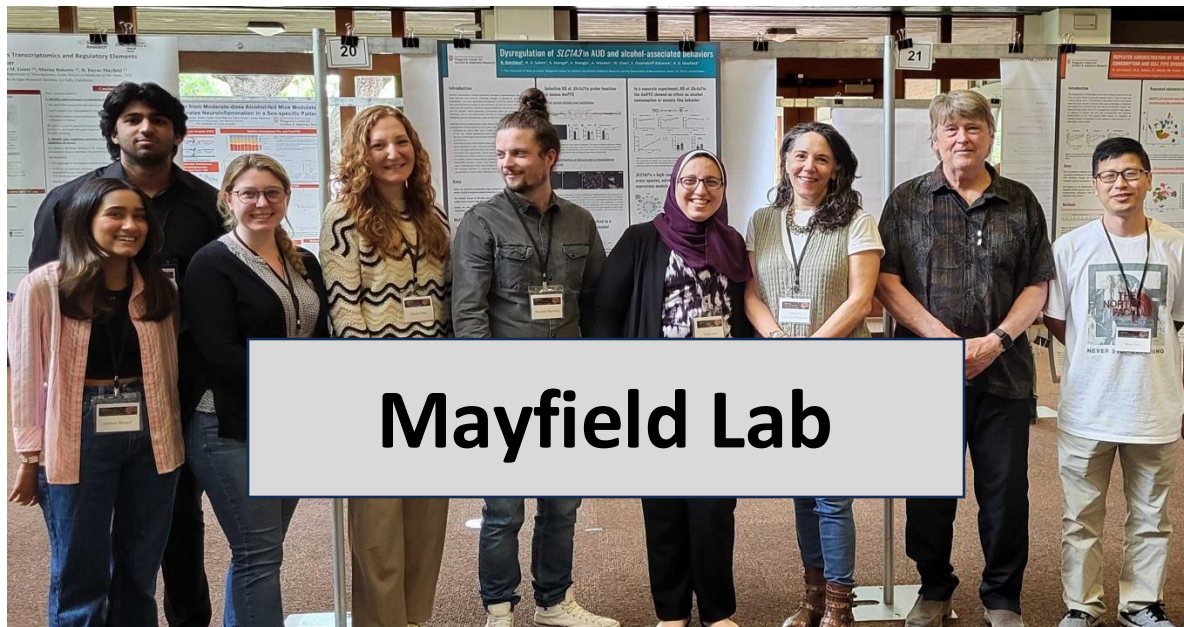
Effect of prior exposure to EtOH on *Glast* KD in the dmPFC



Discussion

- *Glast* is dysregulated following alcohol consumption in both humans and mice, more so than Glt-1 in our data
- KD of *Glast* in the dmPFC does not appear to reliably change EtOH intake or preference, despite the robust inverse correlation between GLAST expression and alcohol intake
- *Glast* KD in the PL appear to have an anxiolytic effect suggesting that *Glast* might play a nuanced role in modulating anxiety-like behaviors

Thank you for your attention!



Mayfield Lab



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