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Whole-brain activity changes in male and female C57BL/6J mice following binge-like alcohol drinking

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Abstract

Binge alcohol drinking is a risk factor for Alcohol Use Disorder (AUD), and though AUD diagnoses are more prevalent in men than women, the gap has recently narrowed. Drinking-in-the-dark (DID) task is a preclinical model for binge alcohol drinking where mice drink to intoxication during a 2–4-hour period. Sex-differences have been seen using the DID model, where female mice tend to drink more, and manipulations of nucleus accumbens core (NAc core) activity differentially impacts ethanol intake in males and females. My project seeks to understand this sex-difference by combining whole-brain c-Fos labeling, a proxy for neural activity, with an intra-NAc core viral retrograde tracer to identify projections to the NAc core that are engaged following binge-like drinking. Male and female C57BL/6J mice (n=17-19/sex/fluid) received 0.5uL AAVrg-hSyn-eGFP bilaterally into NAc core, and underwent a 4-day DID with 20% ethanol or water. We collected samples for determination of blood ethanol concentration (BEC) and brains for c-Fos and retrograde labeling analyses. Whole-brain clearing, immunolabeling, imaging, and registration was completed by Life Canvas Technologies. In our pilot cohort (n=2-3/sex/fluid), on baseline days 1-3 we found an effect of sex (2-way ANOVA, $F(1, 4)=13.83$, $p<0.05$; male: 3.08g/kg ± 0.12 (SEM), female: 4.37g/kg ± 0.31), and a sex-by-day interaction (2-way ANOVA, $F(2,8)=5.470$, $p<0.05$) on 2-hour ethanol, but not water consumption. On day 4, we observed no effect of sex on 4-hour fluid intake or BECs. We found significant increases in c-Fos positive cell density between ethanol and water groups in the ventral basolateral amygdala (BLA, $p<0.05$) and infralimbic cortex (IL, $p<0.05$), with no observed sex differences. Ongoing work will investigate the role of BLA- and IL-NAc core circuits, and analyze co-labeled cFos+GFP neurons to identify the role of sex in the NAc core circuitry engaged during binge-like drinking.