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Strain-dependent contextual fear learning outcomes after acute adolescent ethanol exposure: Examining the role of the dorsal hippocampal transcriptome

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Ethanol disrupts learning and memory, and the severity of these effects may vary by genetic background, sex, and age. To understand how genetics and sex contribute to adolescent learning outcomes after ethanol, we surveyed fear conditioning after ethanol in a panel of inbred mice. Adolescent (PND 38 +/- 3) male and female mice from 9 inbred strains [C57BL/6J, C57BL/6NJ, DBA2/J, 129S1/SvImJ, A/J, BALB/cByJ, BTBR T+ tf/J, C3H/HeJ, and FVB/NJ (The Jackson Laboratory, Bar Harbor, ME; n=9/sex/strain/treatment)] were treated with ethanol (1.5 g/kg, i.p., 20% w/v in 0.9% saline) 15 minutes prior to fear conditioning training. Contextual and cued learning were tested one day later. Contextual fear learning was most sensitive to disruption by pre-training ethanol, with heritable (31%) freezing outcomes dependent upon both strain ($p<0.001$) and sex ($p=0.046$; females more impaired than males). Cued fear learning was also impaired by ethanol, although to a lesser extent than contextual learning, with heritable (18%) freezing outcomes dependent upon strain ($p<0.001$) and not sex. BEC assessment suggested that strain differences in learning after ethanol were not related to ethanol metabolism. Next, we conducted RNA-sequencing of the dorsal hippocampus, a region uniquely involved in contextual learning, in C57BL/6J and DBA/2J strains to identify genetic mechanisms involved in ethanol-associated deficits. We found unique ethanol- and learning-associated transcripts and pathways across strains. Collectively, we demonstrated a genetic basis for learning outcomes after ethanol exposure during adolescence in inbred mice and we have begun identifying neural pathways related to adolescent ethanol-related cognitive deficits.

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