The adult rats after alcohol exposure in a third – trimester model of FASD showed impairment in spatial working memory dependent delayed alternation task

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Introduction

- Fetal Alcohol Spectrum Disorders (FASD) result from exposure to alcohol in utero and their collective prevalence is estimated to be 1-10% globally.
- Alcohol exposure (AE) during the 3rd trimester of human pregnancies could result in underdevelopment of key brain regions critical for working memory, including medial prefrontal cortex (mPFC) and hippocampus (HC).
- Previously, we have shown that in the rodent model of 3rd trimester AE, there is damage to the thalamic nucleus reuniens (Re) (Gursky et al., 2019) which functions as a key intermediary node in the mPFC – HC circuit. We also have shown that Re is critical for mPFC – HC oscillatory synchrony and spatial working memory (SWM) (Layfield et al., 2015 & Hallock et al., 2016).
- We hypothesized that AE during the brain growth spurt in rats would result in SWM deficit in Delayed Alternation (DA) task due to the increase in working memory demand with increasing delay lengths.

Methods and results

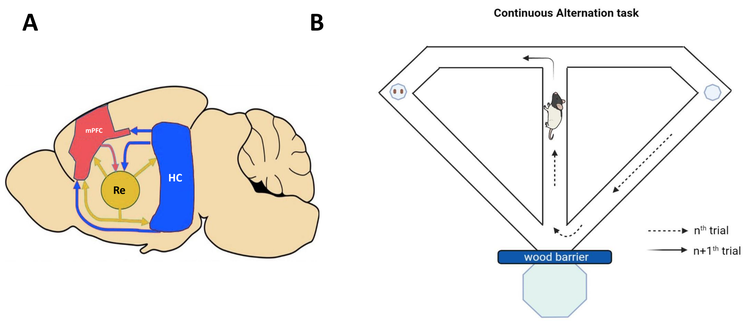

Figure 2 A: **Re is critical for HC – mPFC interaction.** *(modified from Varela et al., 2014)* **B Spatial alternation task schematic**. Rats are rewarded for alternating visits to the left and right goal arms of a T-maze. For Continuous alternation (CA), there is no delay between trials. For delayed alternation (DA), rats are confined to the start box between trials. Our lab has demonstrated that Re inactivation results in a delay-dependent deficit in the DA task (Layfield et al., 2015). The **Continuous Alternation (CA) task** is HC independent (Ainge et al., 2007) and requires low SWM demand.

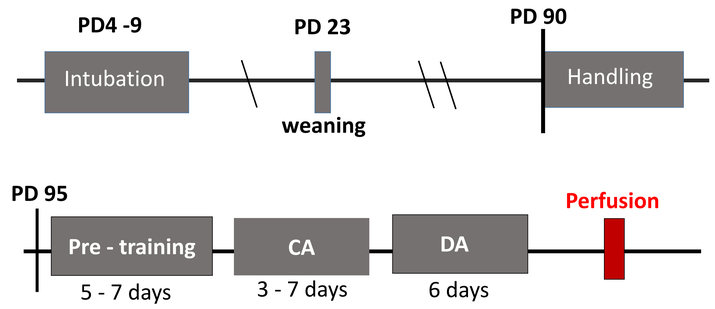

Figure 3 Experimental Timeline. AE pups were given 5.25 g/kg/day ethanol in milk formula via intragastric intubation on postnatal days (PD) 4 – 9. The sham intubated (SI) group received the same intubation as the AE without any liquid. Upon reaching a choice accuracy criterion of 80% for two consecutive days on CA, the rats underwent 6 DA sessions, consisting of 12 each of 10-second (sec), 30 sec, and 60 sec delay trials in a pseudorandom sequence.

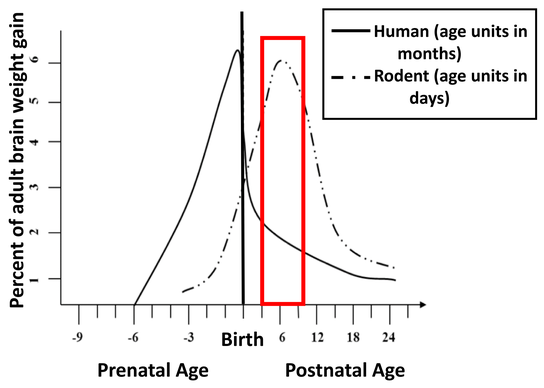

Figure 1
Rodent model of human 3rd trimester AE is equivalent of first 2 postnatal weeks of rodent life. *(modified from Dobbing & Sands, 1979)*

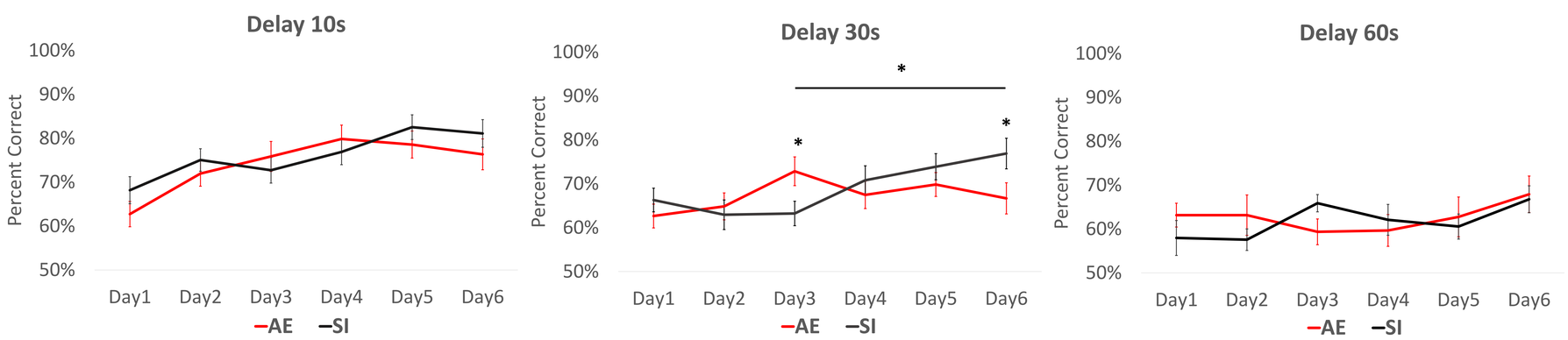

Figure 4 Choice accuracy on the DA task. There were significant interactions between postnatal treatment, delay, and day (**F(10,390)=1.95, *p=.039***). The substantial post hoc analysis demonstrated that there was a significant interaction between day and postnatal treatment during delay 30s only (**F(5,195)=2.70, p=.022**). For the 10 s delay trials, both AE and SI groups showed improvement across days, whereas for the 60 s delay trials, both groups performed uniformly poorly across days. There were significant main effects of day **(F(5,185)=7.93, *p<.001)*** and delay **(F(2,74)=33.63, *p<.001***). AE male (n= 10); AE female (n=9); SI male (n=13); SI female (n= 9).

Discussion and Conclusions

- The SI group showed consistent improvement across session on the 30 sec delay trials, whereas the AE group did not, supporting the hypothesis that AE during the brain growth spurt leads to SWM deficits in adulthood.
- For the 10 sec delay trials, both AE and SI groups showed improvement across days, whereas for the 60 sec delay trials, both groups performed uniformly poorly across days. These results highlight the importance of utilizing varying delay lengths to reveal SWM deficits in AE models.
- Future studies will build on the current results by examining the effects of early AE on SWM – related functional interactions within the HC – Re – mPFC circuit.

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