

ETHANOL MODULATES THE SPATIO-TEMPORAL EXPLORATION PATTERNS
BASED ON HOMEBASE DYNAMICS IN TWO OUTBRED ZEBRAFISH
FOLLOWING REPEATED EXPOSITION

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INTRODUCTION: Ethanol (EtOH) is one of the most widely consumed substance, affecting neurobehavioral functions depending on multiple environmental and biological factors. Several circumstances affect EtOH-mediated toxicity, such as genetic susceptibility, psychological stress, and exposure to early life trauma. Moreover, the effects of EtOH often occurs in dose-dependent manner. In zebrafish, EtOH modulates anxiety-like behaviors in novelty-based paradigms, while the potential role of biological sex and populational variability in the exploratory dynamics in the open field test (OFT) is unknown. **OBJETIVE:** Here, we aimed to explore whether a repeated EtOH exposure protocol modulates the spatio-temporal exploration and homebase-related parameters in a population-and sex-dependent manner. **METHODOLOGY:** Male and female fish from the short-fin (SF) and leopard (LEO) phenotypes were exposed, separately, to EtOH (1 % v/v, 20 min per day) during 7 days. On the 8th day, a 30 min trial in the OFT was performed in a transparent circular-shaped arena (25 cm diameter) filled with dechlorinated water and the behavior recorded with a top located web cam. We assessed the locomotor patterns as well as behavior in the periphery, homebase index, and exploration mechanism, and ran a PCA to understand the main behaviors that contributes to behavioral outcomes. **RESULTS:** We verified significant populational differences in the baseline spatio-temporal exploration patterns, supporting a pronounced anxiety in LEO, with a higher homebase index compared to SF. We also found sex-dependent differences in EtOH sensitivity, where SF was more sensitive to EtOH, especially females, which showed marked alterations in thigmotaxis and homebase occupancy. Conversely, only LEO female subjects showed increased center occupancy following

EtOH. Principal component analysis (PCA) data reinforced that each population employs distinct behavioral strategies to acclimate to and explore the environment. Interestingly, a lack of significant effects in EtOH-exposed LEO zebrafish corroborates with the lower sensitivity to EtOH in this population. CONCLUSION: Our findings support the utility of zebrafish-based models to assess how EtOH influences the exploratory profile in the OFT to elucidate potential differences of sex and in a translational perspective.

Keywords: Ethanol; Anxiety; Exploration; Zebrafish; Biological factors