Effects of Sex and Ethanol on Approach-Avoidance Conflict Resolution: Including Females in a Preclinical Model of Alcohol Use Disorder

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Introduction:

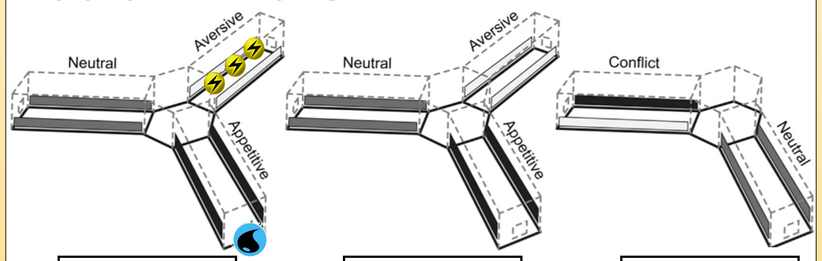
- Alcohol use disorder (AUD) is characterized by excessive alcohol consumption, inability to control alcohol seeking during unavailability, and compulsive-seeking[1].
- AUD prevalence in females is increasing and they are more susceptible than males to the negative health consequences of alcohol use[2]. However, they are underrepresented in preclinical models of AUD.
- Cocaine pre-exposed animals showed greater tendencies to approach conflicting cues of appetitive and aversive valences compared to cocaine naïve animals[3].
- This study aimed to include females in assessing the effects of ethanol to approach-avoidance decision-making and in evaluating a proposed preclinical model of AUD.

Methods:

Subjects: 40 Long Evans rats, 20 males and 20 females.

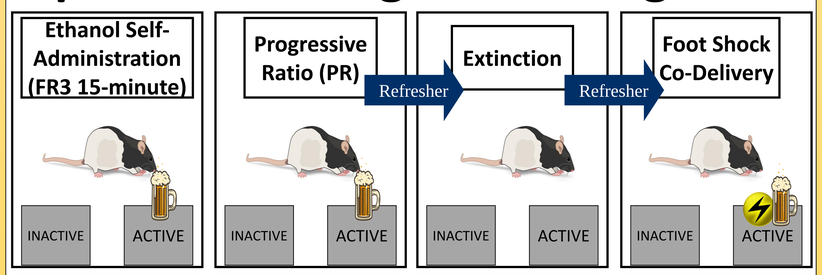
Radial Y-Maze:

Half of the animals self-administered ethanol in their home cages for 5 weeks prior to this test.



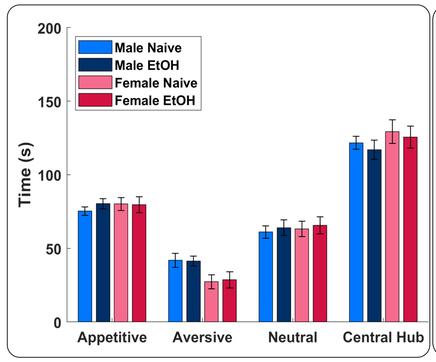
Conditioning	Acquisition Test	Conflict Test
Foot shock Sucrose	No outcomes presented	Shock & sucrose cues in conflict arm

Operant Training & Challenges:



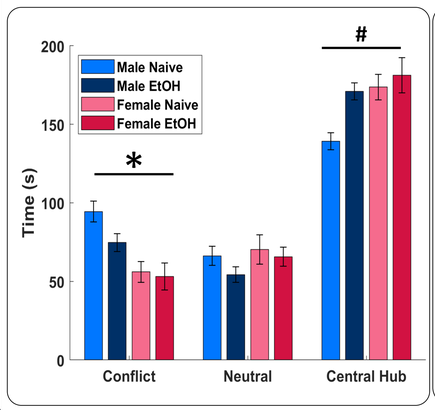
3x Active -> Ethanol 3x Inactive -> levers retract	Increasing lever presses required for each dose of ethanol	4 non-reinforced FR3 15-minute sessions	5 sessions with increasing shock intensities

Y-Maze Acquisition Test



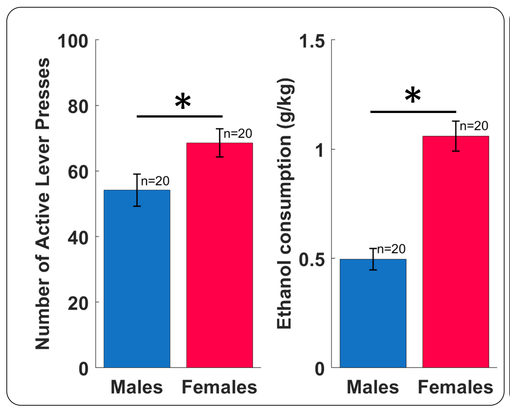
- All animals associated the cues appropriately to the respective appetitive, aversive, and neutral outcomes independent of sex and ethanol history.

Y-Maze Acquisition Test



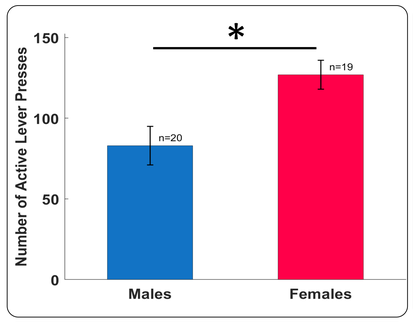
- Males spent more time in the conflict arm then females.
- Ethanol pre-exposed animals spent more time in central hub than the ethanol naïve animals.
- * effect of sex for that arm
- # effect of ethanol history for that arm

Ethanol Self-Administration



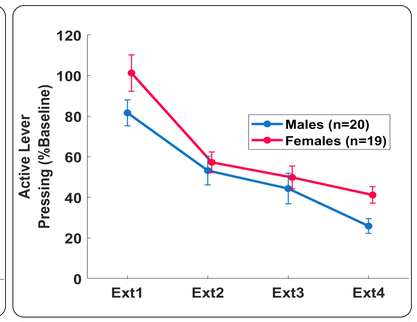
- Females lever pressed more and consumed more ethanol (corrected to body weight) than males during the FR3 15-minute self-administration training sessions.

Progressive Ratio



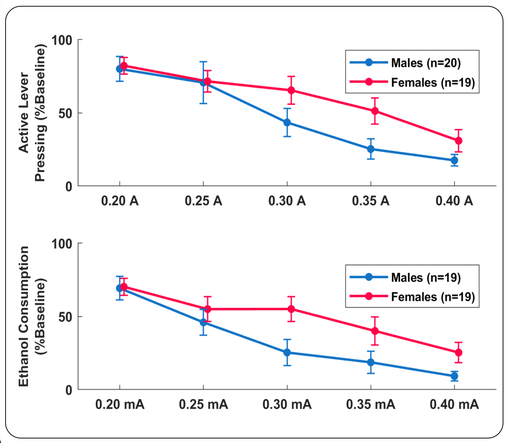
- Females lever pressed significantly more and obtained higher breakpoints (data not shown) than males.

Extinction



- There was a trend for females to retain greater percent baseline lever pressing than males.

Resistance to Foot Shock



- Both sexes had similar percent baseline lever pressing.
- There was a trend for females to consume more ethanol at higher foot shock intensities than males.

Discussion:

- Females relative to males displayed reduced approach of conflict, although ethanol history did not affect approach-avoidance decision making unlike cocaine.
- Females consumed more ethanol, displayed greater motivation, and had a trend to be more persistent in ethanol seeking and more resistant to extinction and foot shock compared to males.
- Future directions of interest include analyses of ventral hippocampal projection activity to the median prefrontal cortex and nucleus accumbens which are involved in approach-avoidance decision making and affected by ethanol.

References: 1. Koob, G. F. Theoretical frameworks and mechanistic aspects of alcohol addiction: Alcohol addiction as a reward deficit disorder. Curr. Top. Behav. Neurosci. 13, 3–30 (2011).
2. Milic, J. et al. Menopause, ageing, and alcohol use disorders in women. Maturitas 111, 100–109 (2018).
3. Nguyen, D., Schumacher, A., Erb, S. & Ito, R. Aberrant approach-avoidance conflict resolution following repeated cocaine pre-exposure. Psychopharmacology (Berl). 232, 3573–3583 (2015).

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