

Sex Differences in Fear Regulation Across Multiple Safety Protocols

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Introduction

- Research in emotional regulation across sexes is limited, since typically only male subjects are used
- Goal replicate past experiments' outcomes, with a modified protocol to better support single neuron recording analyses and other new techniques
- Long Evans rats were assessed for fear and reward seeking behaviors during cues associated with administration of sucrose, foot shock or no outcome, and compared with a previous protocol
- Neuronal correlates of behavioral sex differences observed to a safety cue could provide novel insights into the neural underpinnings of maladaptive fear across the sexes → fear regulation disorders like PTSD

Methods



Recorded in Behavioral Boxes



Data Analysis 2 Way RM ANOVA For Each Session (Cue, Sex)



FRS ORIGINAL **Paradigm Sessions**

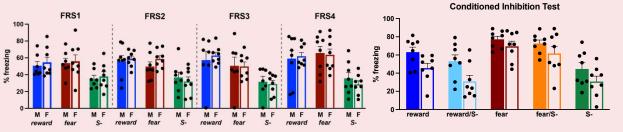
- 6 Reward -> ____(R+) • 4 FRS (Fear; Reward; S-)
- 15 Auditory A -> (R+)
- 4 Auditory B -> // (F+) • 25 Visual -> (S-)
- Cl (Conditioned Inhibition)
- 9 Auditory A -> (R+) • 4 Auditory B -> /Z (F+)
- 10 Visual + A -> (RS-)
- 10 Visual -> (S-) • 11 Visual + B -> (FS-)

FRS ADJUSTED **Paradigm Sessions**

- 4 Reward -> (R+) • 4 FRS (Fear; Reward; S-)
- 15 Auditory A -> ____(R+)
- 8 Auditory B -> // (F+) • 20 Visual -> (S-) CI (Conditioned Inhibition)
- 9 Auditory A -> ____ (R+) • 8 Auditory B -> (F+)
- 10 Visual -> (S-) • 11 Visual + A -> (RS-)
- 10 Visual + B -> (FS-)

Freezing Results Conditioned Inhibition Test FRS1 FRS3 MF MF MF MF M F S-MF M F Sreward fear reward fear reward

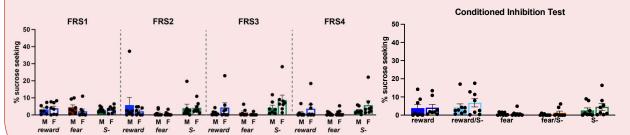
Original FRS Paradigm showed good fear discrimination in both males and females. However, only males showed significant conditioned inhibition of fear to the combined fear/S- cue. ****p<0.0001 fear cue was higher than all other cues, M. males, F. females.



Adjusted FRS Paradigm showed generalized freezing to all cue in both sexes across all FRS and CI sessions. During CI, neither males nor females showed conditioned inhibition to the fear/S- cue. However, females did show higher freezing to the fear cue vs reward cue; males did not. M, males. F, females

Sucrose Seeking Results Conditioned Inhibition Test S-

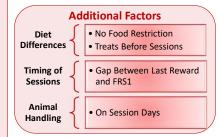
Original FRS Paradigm showed good sucrose discrimination in both males and females. Both males and females showed significant conditioned inhibition of sucrose seeking to the combined reward/S- cue. ****p<0.0001 reward cue was higher than all other cues. M, males. F, females.

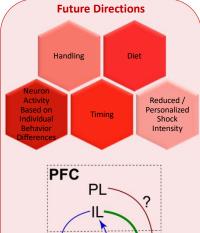


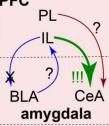
Adjusted FRS Paradigm showed very little sucrose seeking in both sexes across all sessions. This is likely due to the generalized freezing seen to all cues.

Take Home Messages

- 4 shock trials (Original) → significant regulation of fear in the presence of S- cue for males, but not females.
- 8 shock trials (Adjusted) -> generalization of fear for both sexes to all cues
- Despite the fear generalization, females learned to freeze more to the fear cue Vs. reward cue, while males froze equally to both.







Partial safety circuit of Amygdala and Prefrontal Cortex. IL → CeA required for expression of safety behavior IL → BLA not required for safety expression BLA → IL and PL → CeA are projections of interest, which may be tested by the presented protocols

References

Greiner EM, Müller I, Norris MR, Ng KH, Sangha S (2019), Sex differences in fear regulation and reward seeking behaviors in a fear-safety-reward discrimination task. Behavioural Brain Research, 368: 111903.