



# EFFECTS OF STRESS PRIOR TO COCAINE SELF-ADMINISTRATION ON SEEKING BEHAVIOR

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## INTRODUCTION

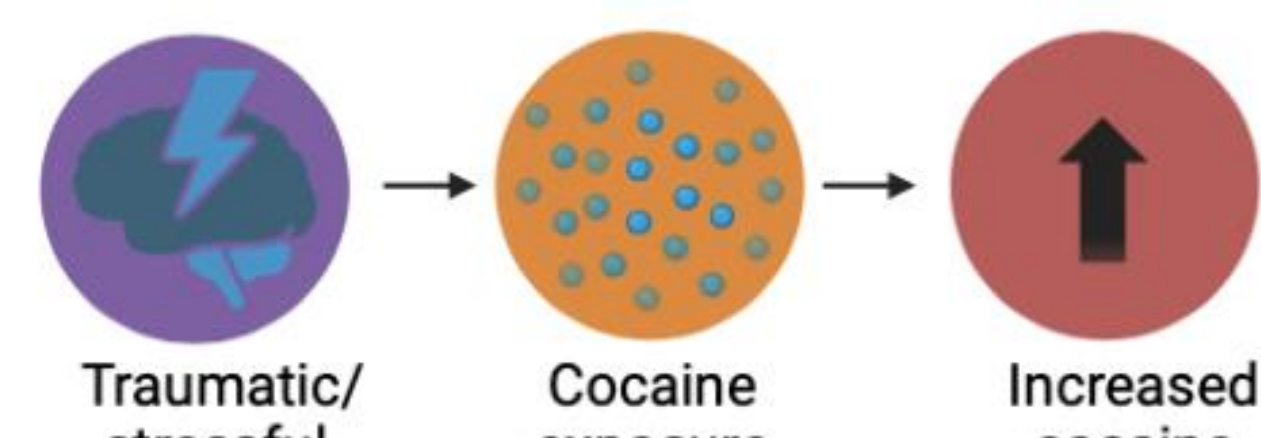
- In 2020, it was reported that 37.9 million adults aged 18 or older in the United States suffered from substance use disorder (SUD), and among these people, 17 million adults (45%) exhibited mental illness (SAMHSA, 2021).
- Clinical research has shown that stress plays a role in cocaine addiction by identifying co-occurrence between cocaine use disorder (CUD) and trauma/stressor-related disorders (Perkonig et al., 2010).
- Statistics show that 34% of trauma-exposed individuals meet lifetime CUD criteria (Khoury et al., 2010).

## AIM

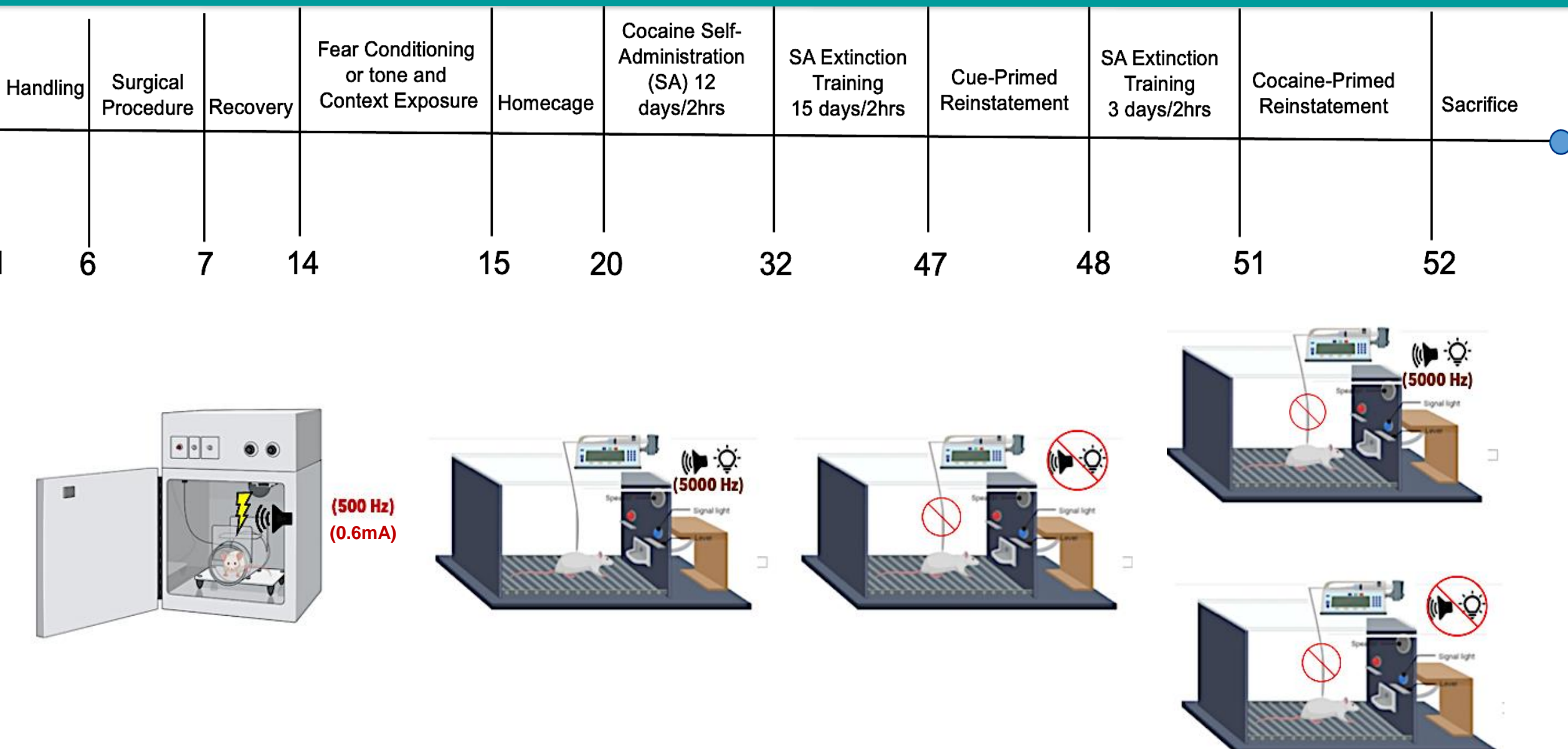
Determine the influence of stress on cocaine acquisition and seeking behavior in male and female rats

## HYPOTHESIS

Male and female rats exposed to fear conditioning prior to cocaine acquisition will show an increase cocaine-seeking behavior and drug consumption compared to non-stressed rats.

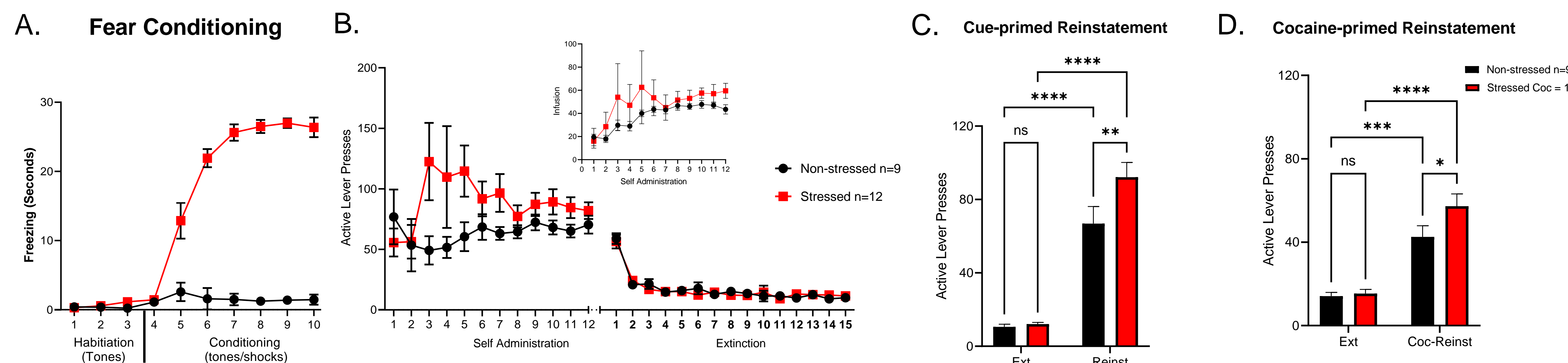


## METHODS



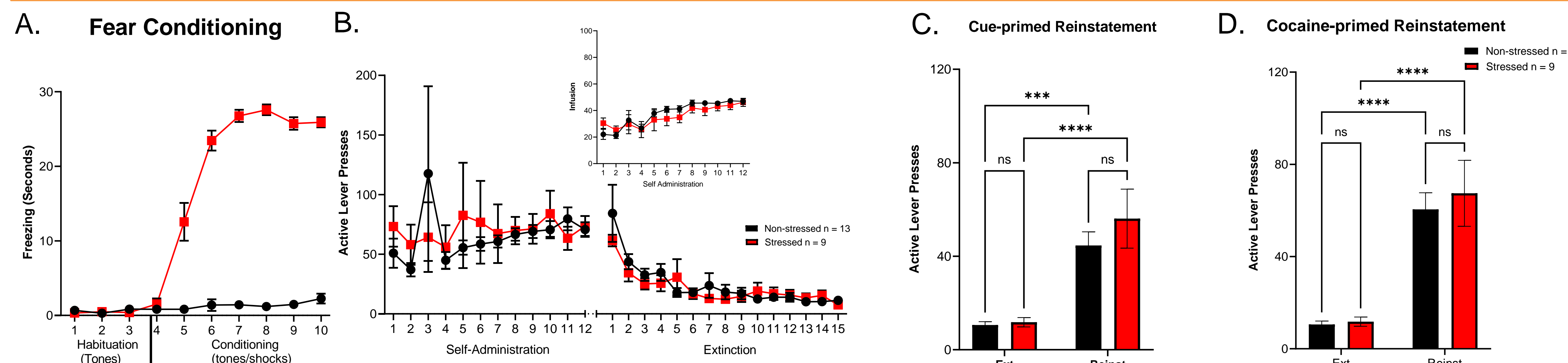
## RESULTS

### Male Behavioral Results



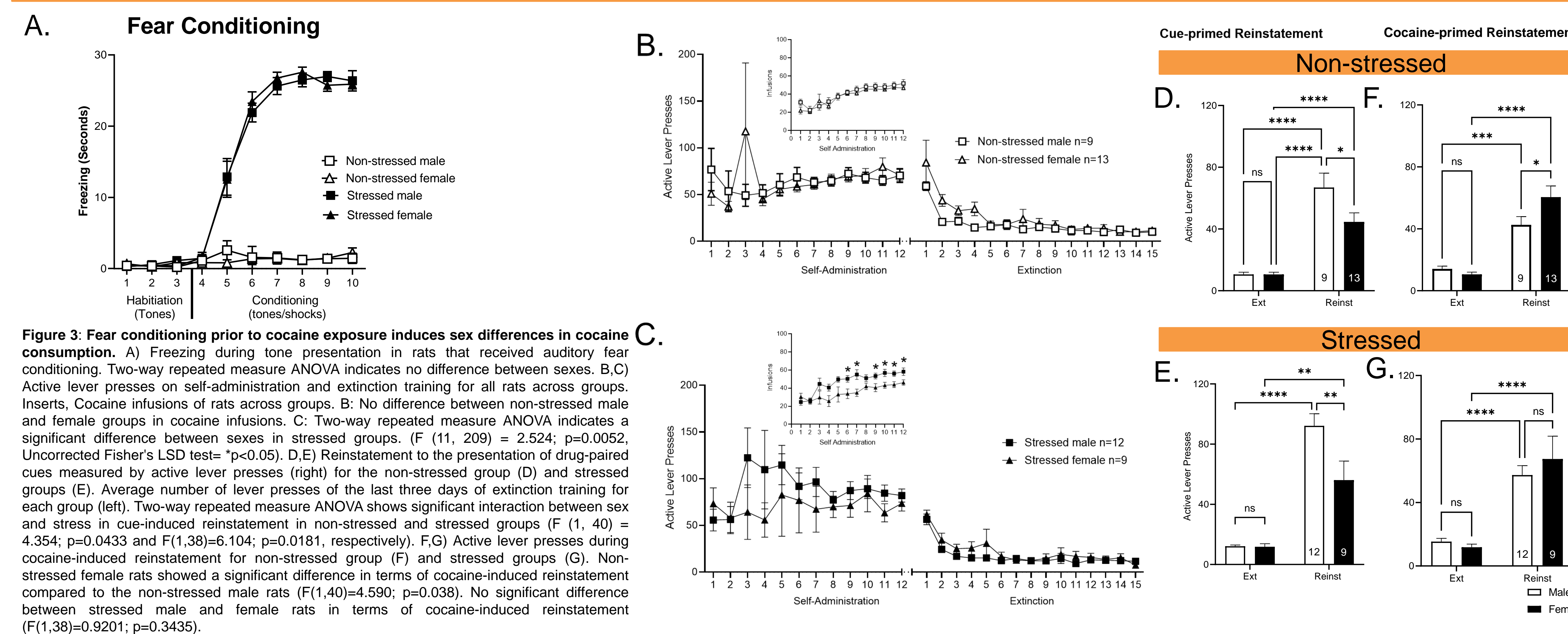
**Figure 1. Fear conditioning prior to cocaine exposure increases cue- and cocaine-induced reinstatement in male rats.** A) Freezing during tone presentation in rats that received auditory fear conditioning. B) Active lever presses on self-administration and extinction training for all rats across groups. Insert, Cocaine infusions of rats across groups. C) Reinstatement to the presentation of drug-paired cues measured by active lever presses (right). Average number of lever presses of the last three days of extinction training for each group (left). A 2-way ANOVA with multiple comparison analysis shows a main effect on cue-induced reinstatement of fear conditioned (stressed) vs. context-exposure (non-stressed) groups ( $F(1, 40) = 0.6445$ ;  $p=0.4268$ ). F) Reinstatement to drug injection measured by active lever presses (right). Average number of lever presses of the last three days of extinction training for each group (left). A 2-way ANOVA with multiple comparison analysis shows a significant difference in cocaine-induced reinstatement of fear conditioned rats compared to context exposure rats ( $p<0.05$ , Uncorrected Fisher's LSD test).

### Female Behavioral Results



**Figure 2. Fear conditioning prior to cocaine exposure did not alter cue- and cocaine-induced reinstatement in female rats.** A) Freezing during tone presentation in rats that received auditory fear conditioning. B) Active lever presses on self-administration and extinction training for all rats across groups. Insert, Cocaine infusions of rats across groups. C) Reinstatement to the presentation of drug-paired cues measured by active lever presses (right). Average number of lever presses of the last three days of extinction training for each group (left). A 2-way ANOVA with multiple comparison analysis shows no significant difference in cue-induced reinstatement of fear-conditioned (stressed) vs. context-exposure (non-stressed) groups ( $F(1, 40) = 0.6445$ ;  $p=0.4268$ ). F) Reinstatement to drug injection measured by active lever presses (right). Average number of lever presses of the last three days of extinction training for each group (left). A 2-way ANOVA with multiple comparison analysis shows no difference in cocaine-induced reinstatement of fear-conditioned rats compared to context-exposure rats ( $F(1, 40) = 0.1508$ ;  $p=0.6998$ ).

### Sex Differences



**Figure 3: Fear conditioning prior to cocaine exposure induces sex differences in cocaine consumption.** A) Freezing during tone presentation in rats that received auditory fear conditioning. Two-way repeated measure ANOVA indicates no difference between sexes. B,C) Active lever presses on self-administration and extinction training for all rats across groups. Inserts, Cocaine infusions of rats across groups. B) No difference between non-stressed male and female groups in cocaine infusions. C. Two-way repeated measure ANOVA indicates a significant difference between sexes in stressed groups. ( $F(11, 209) = 2.524$ ;  $p=0.0052$ , Uncorrected Fisher's LSD test;  $p<0.05$ ). D,E) Reinstatement to the presentation of drug-paired cues measured by active lever presses (right) for the non-stressed group (D) and stressed groups (E). Average number of lever presses of the last three days of extinction training for each group (left). Two-way repeated measure ANOVA shows significant interaction between sex and stress in cue-induced reinstatement in non-stressed and stressed groups ( $F(1, 40) = 4.354$ ;  $p=0.0433$  and  $F(1, 38)=6.104$ ;  $p=0.0181$ , respectively). F,G) Active lever presses during cocaine-induced reinstatement for non-stressed group (F) and stressed groups (G). Non-stressed female rats showed a significant difference in terms of cocaine-induced reinstatement compared to the non-stressed male rats ( $F(1,40)=4.590$ ;  $p=0.038$ ). No significant difference between stressed male and female rats in terms of cocaine-induced reinstatement ( $F(1,38)=0.9201$ ;  $p=0.3435$ ).

## SUMMARY

- Preliminary data shows that fear conditioning prior to cocaine self-administration increases cue- and cocaine-primed reinstatement in male rats compared to female rats.
- Non-stressed and stressed male rats have higher cue-induced reinstatement compared to female groups.
- Interestingly, stressed male rats have higher cocaine consumption compared to stressed female rats.
- These data demonstrate that with or without fear conditioning prior to cocaine exposure (2 hrs), the male rats have higher cocaine seeking compared to female rats.
- Our results suggest that a traumatic event may influence the transition from the recreational use of cocaine to the development of cocaine use disorder (CUD).

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