



Introduction

- Exacerbated fear responses following extreme stress are observed in both humans and rodents. This is especially pronounced in cases of human psychiatric conditions like post-traumatic stress disorder (PTSD).
- PTSD is two-to-three times more prevalent in women than men (McLean et al., 2011).
- There has been difficulty in identifying a suitable experimental design in the rodent model that replicates the sexual dimorphism of PTSD in the human species. The stress enhanced fear learning (SEFL) is a commonly-used approach, but typically does not replicate the sexual dimorphism observed in humans (Nishimura et al., 2022).
- Inhibitory avoidance has well-documented sex differences, with females typically showing increased generalization relative to males (e.g., Lynch et al., 2013).
- The goal of the present experiments was to apply the SEFL paradigm to inhibitory avoidance in order to examine sex differences in learning following stress.

Methods

Subjects.

Experiment 1: Long Evans rats (n=24/12 per sex), PND 60-70.
Experiment 2: Female Long Evans rats (n= 15), PND 60-70.

Behavior.

Experimental phases were each separated by 24 hours.

Stress. Following a 3-minute baseline period, animals received 15 1.0 mA 1-second shocks separated by a 6-minute intertrial interval. Animals were removed 3 minutes following the last footshock. Animals in the No Stress condition were placed in the chamber for an equivalent amount of time (90 minutes) but received no footshocks.

Training. Animals were placed on the left side of a two-compartment chamber, marked white (left side) and black (right side). After 30 s, the guillotine door was raised. When all four paws crossed to the right side of the compartment, the guillotine door closed. 5 s after the door closed, a 2-s, 0.7 mA shock was delivered. The animal was removed from the chamber 30 s following the shock.

Extinction (Experiment 2). Animals were placed in the black side of the chamber for 10 min.

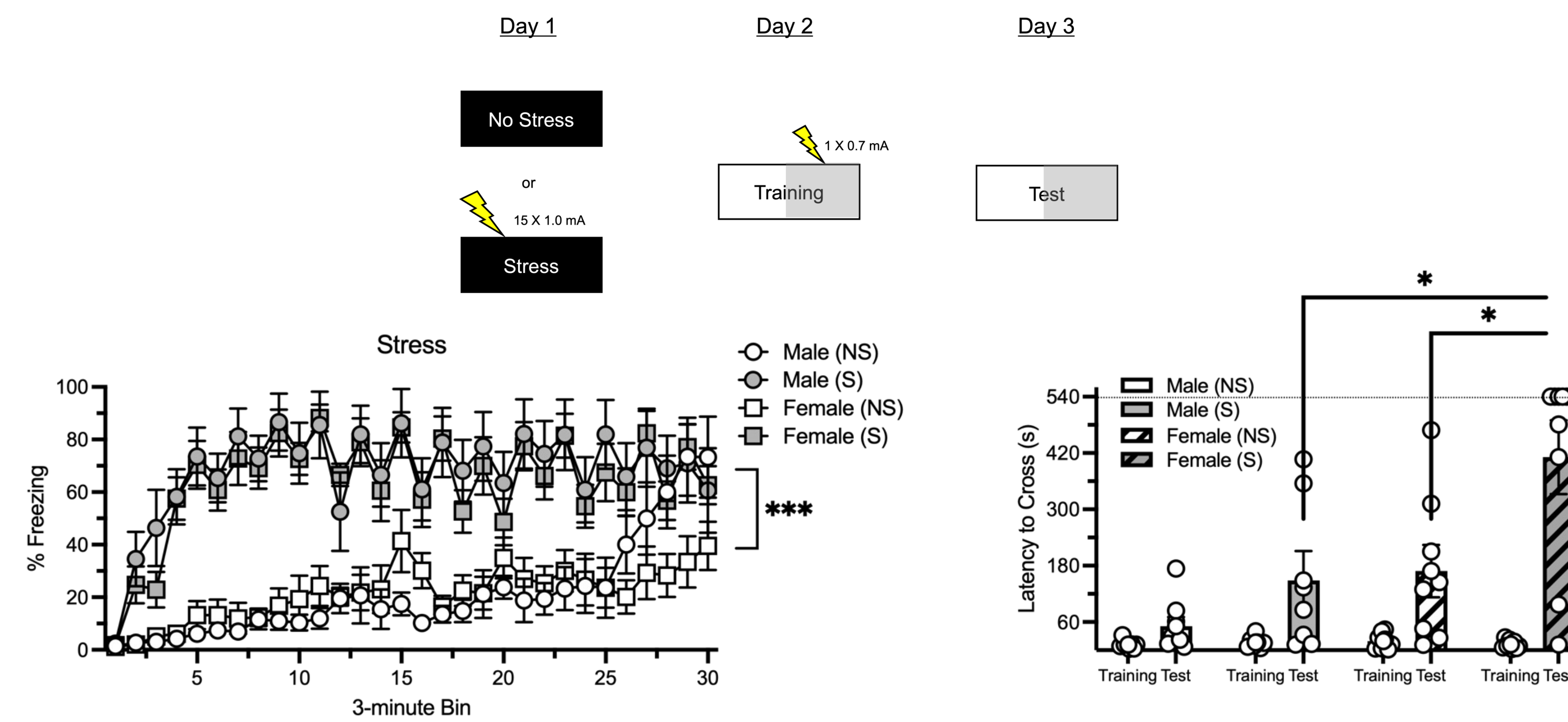
Testing. As in training, the guillotine door was raised after 30 s. This remained open for 540 s and no shocks were delivered. Latency to cross from the white side to the black was recorded and animals that did not cross were given a maximum score of 540 s. After crossing or after 540 seconds (whichever came first), animals were removed from the chamber.

Immunofluorescence.

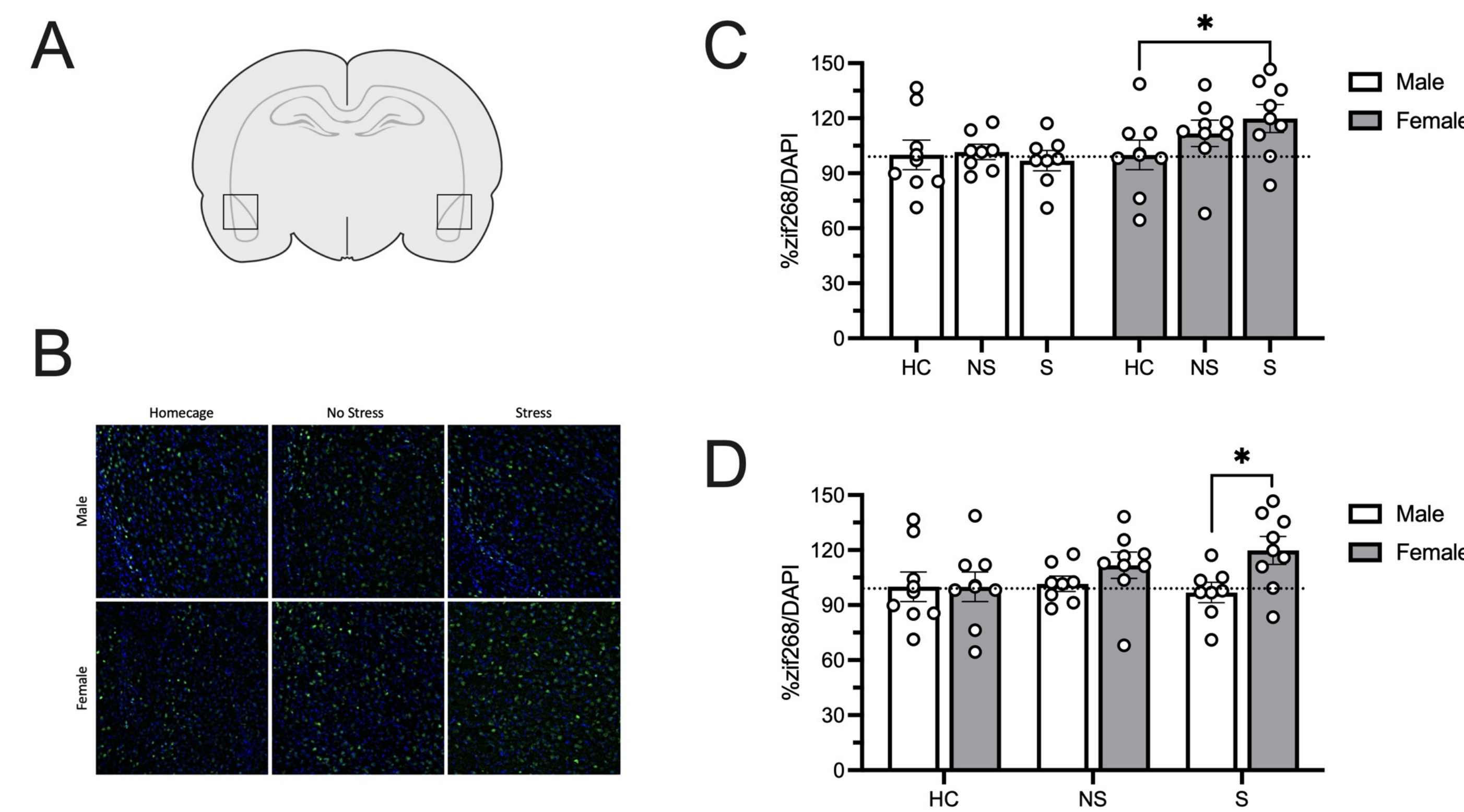
Brains were removed and flash frozen 65 minutes following the start of testing. Tissue was incubated with zif268/EGR-1 antibody DAPI in order to measure immediate early gene expression in the basolateral amygdala.

Results

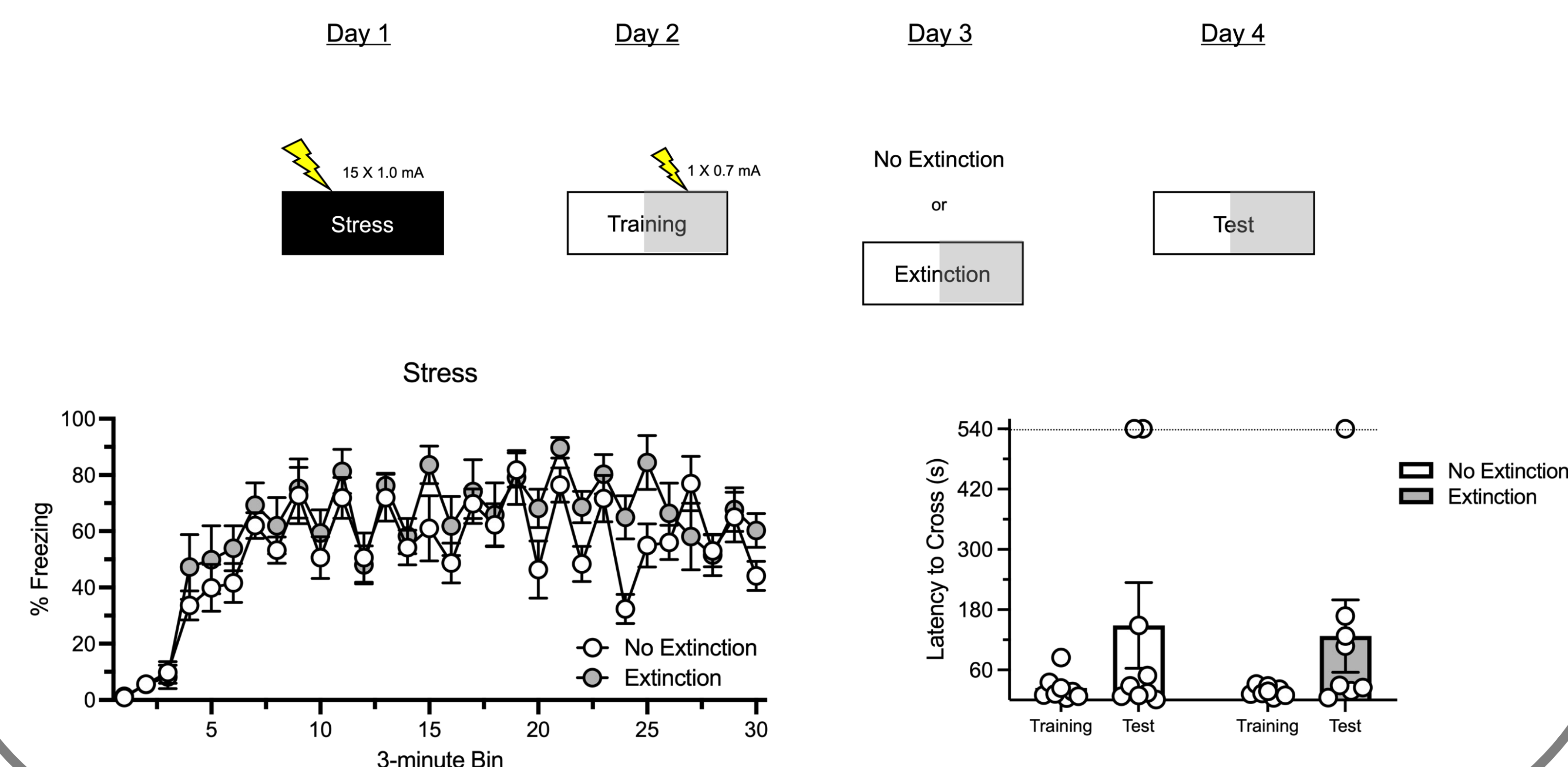
Both sexes of shocked rats exhibited greater rates of freezing during stress, but females that received prior stress displayed significantly longer latencies at testing.



Female, but not male, stressed rats showed increased zif268 expression in the BLA.



Extinction did not impact latency to cross during testing.



Conclusions

Inhibitory avoidance learning was more robust in female rats that received prior stress relative to non-stressed females and stressed males, respectively. Thus, only females demonstrated stress-enhanced avoidance learning.

Female rats that received prior stress had greater zif268 expression in the basolateral amygdala; this was not the case in males. This corresponds to prior work that demonstrates that neural activity assessed through zif268 expression corresponds with fear behavior (Bonanno et al., 2023).

Stress-enhanced avoidance learning is not affected by extinction learning, with extinction failing to reduce latency to cross relative to a group that does not receive extinction.

These results provide initial evidence that stress-enhanced avoidance learning might be a more effective method than SEFL to investigate the bifurcation of behavioral and neural sex differences in aversive learning following stress.

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References

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