

# Impact of Context Manipulation Prior to Fear Extinction in Adolescent Mice

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## Aim

To determine the extent to which altering contextual factors such as the type of conditioning chamber and the presence of a tone impacts fear extinction learning and retention.

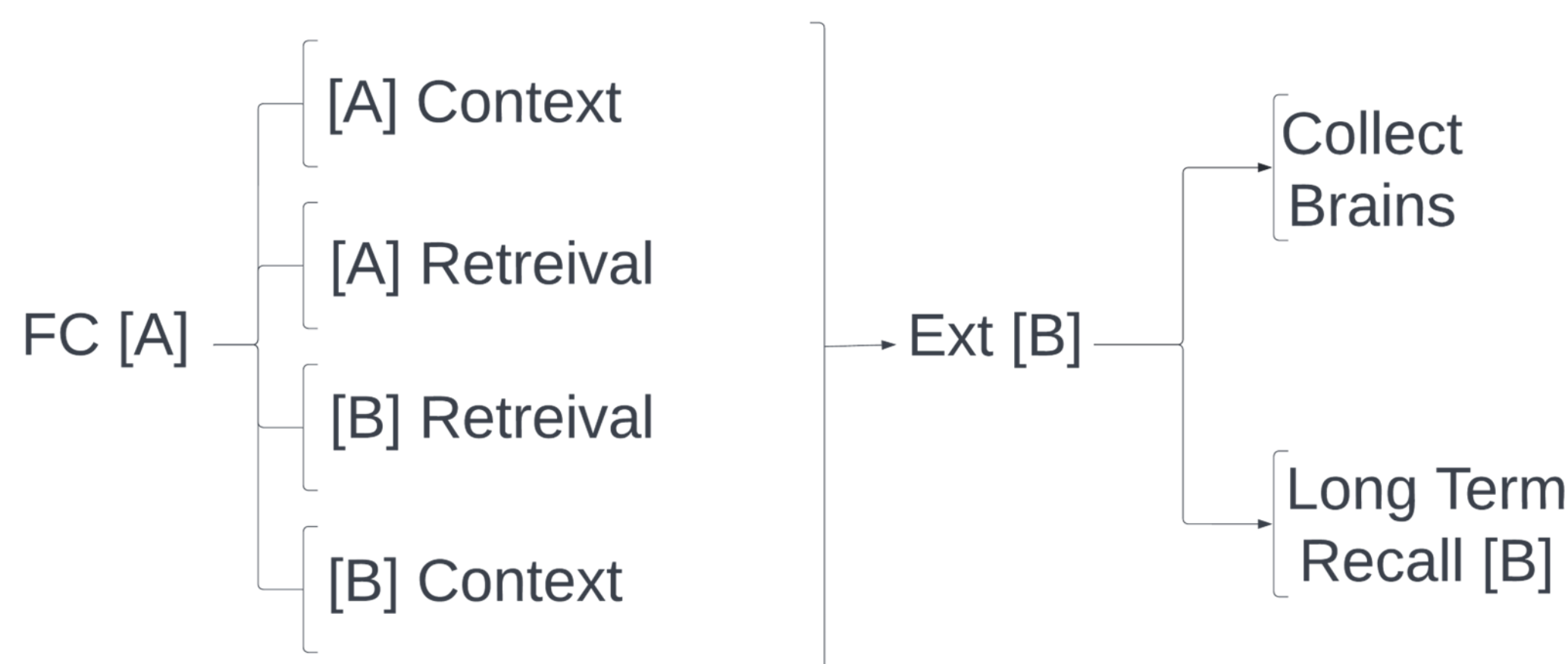
## Introduction

Cognitive behavior therapies are an additional treatment option for anxiety-related disorders, but despite the recent prevalence of adolescent anxiety disorder diagnoses, they are primarily ineffective in adolescents<sup>2</sup>.

Neurological changes that occur during adolescence, such as the reorganization of the prefrontal cortex and amygdala result in altered fear regulation compared to adults<sup>1</sup>. Therefore, research must specifically target the adolescent population.

Understanding how context manipulation impacts the effectiveness of extinction-based therapies greatly benefits the refinement of possible treatments for adolescents.

## Methods



### Subjects:

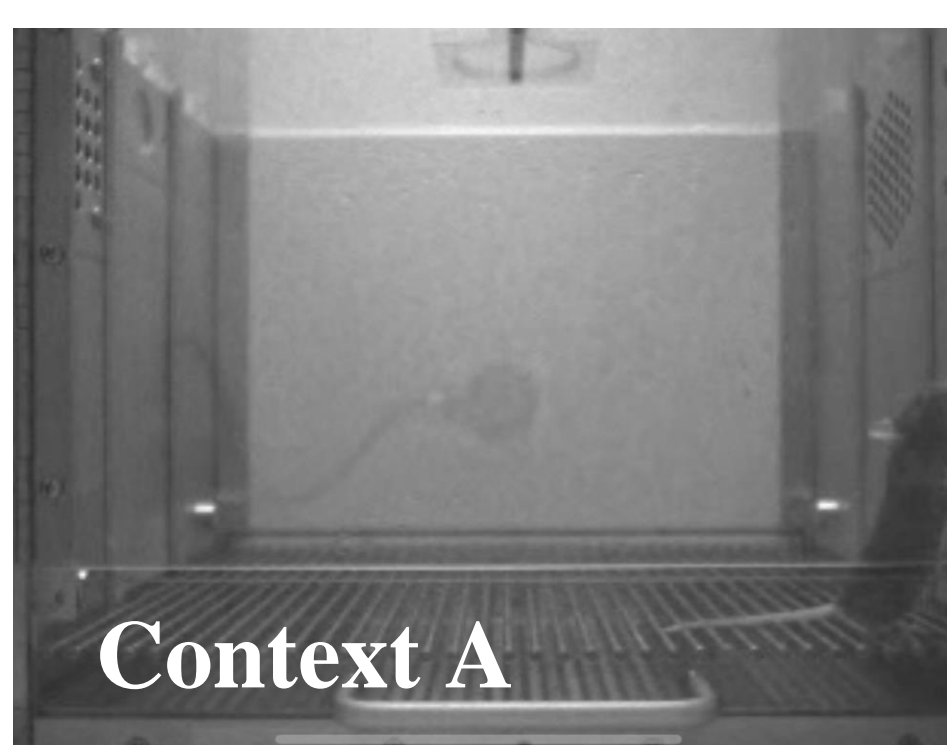
- Adolescent (PND 32-36) male and female C57BL6J mice

### Apparatus:

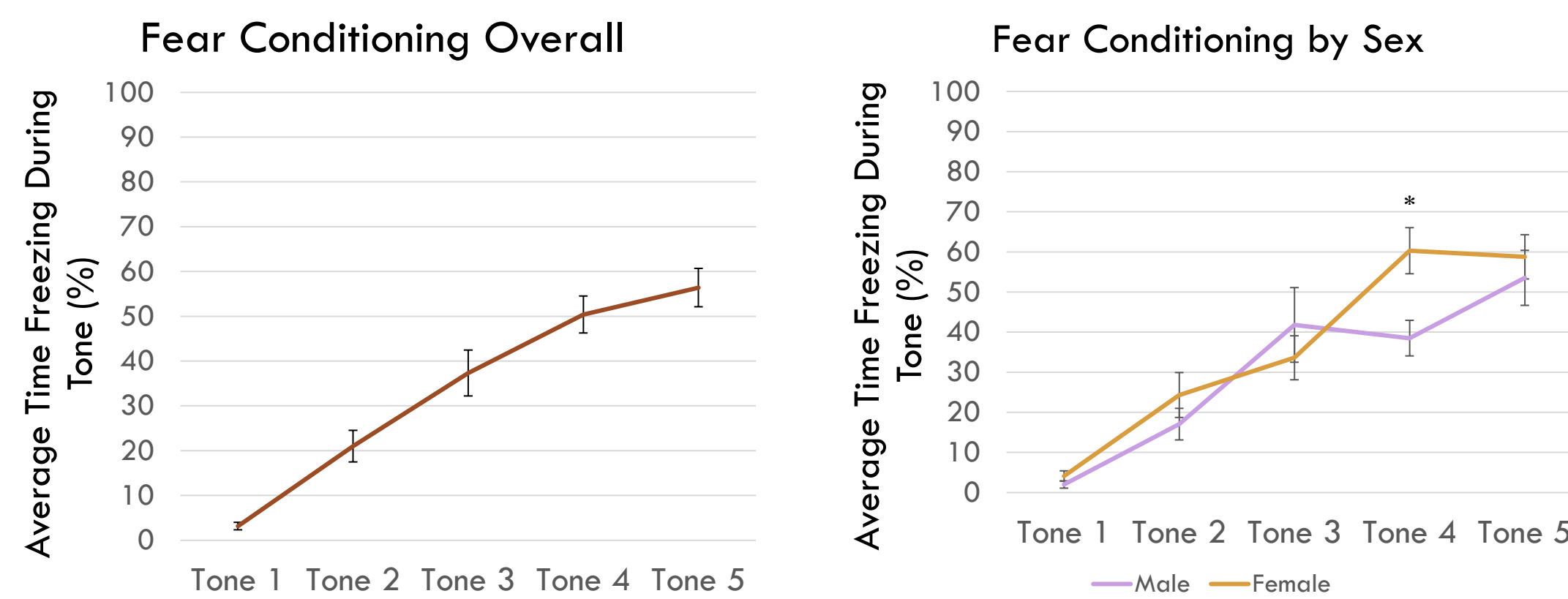
- Med Associates Conditioning Chambers (Contexts A and B)

### Behavioral Protocols:

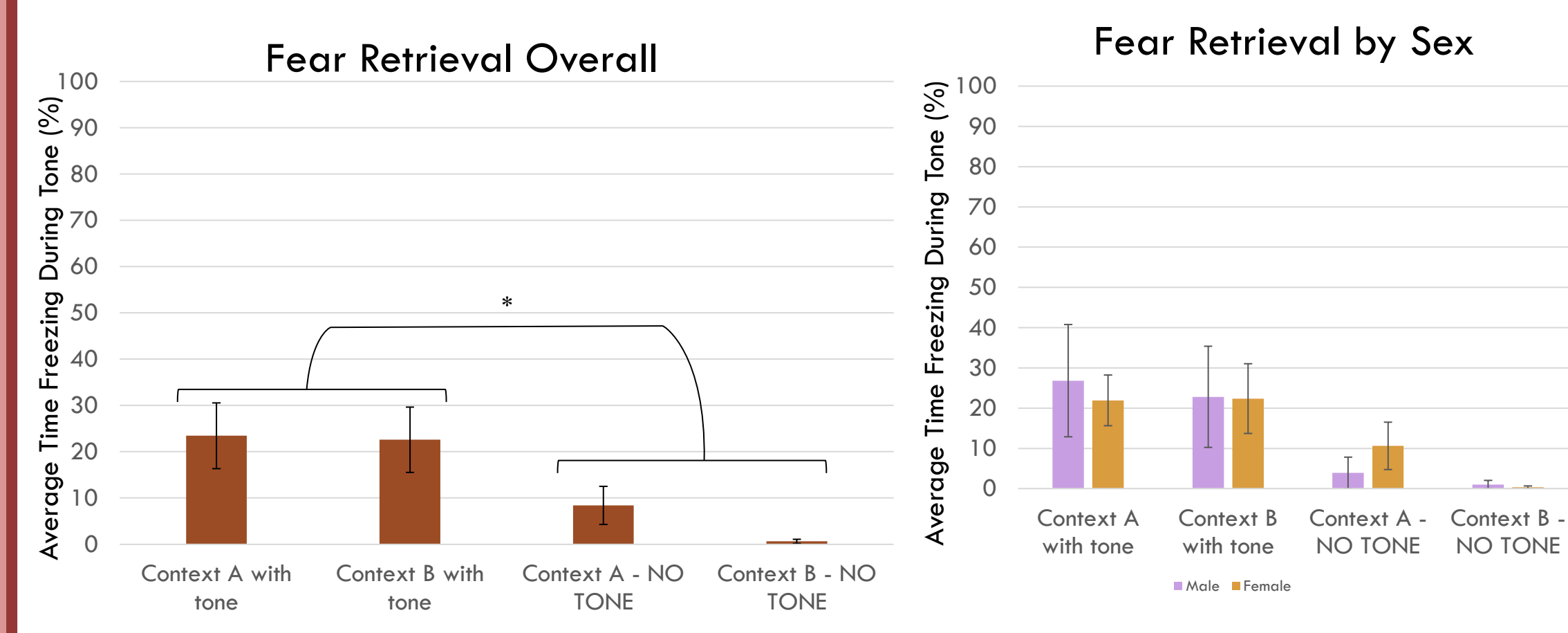
- Fear conditioning (Day 1, Context A):
  - 5 tones- 5kHz, 80 dB, 20 secs; foot shock- 0.5 mA, 1 sec
- Fear retrieval (Day 2, Randomly sorted into context manipulation groups):
  - Context A with tone, Context A with no tone, Context B with tone, Context B with no tone
  - 3 mins total with 20 sec tone if applicable
- Extinction (Day 3 & 4, Context B)
  - 20 tones- 5kHz, 80 dB, 20 secs; no foot shock
- Long term fear recall (2 weeks post extinction, Context B)
  - 3 mins total with 20 sec tone if applicable



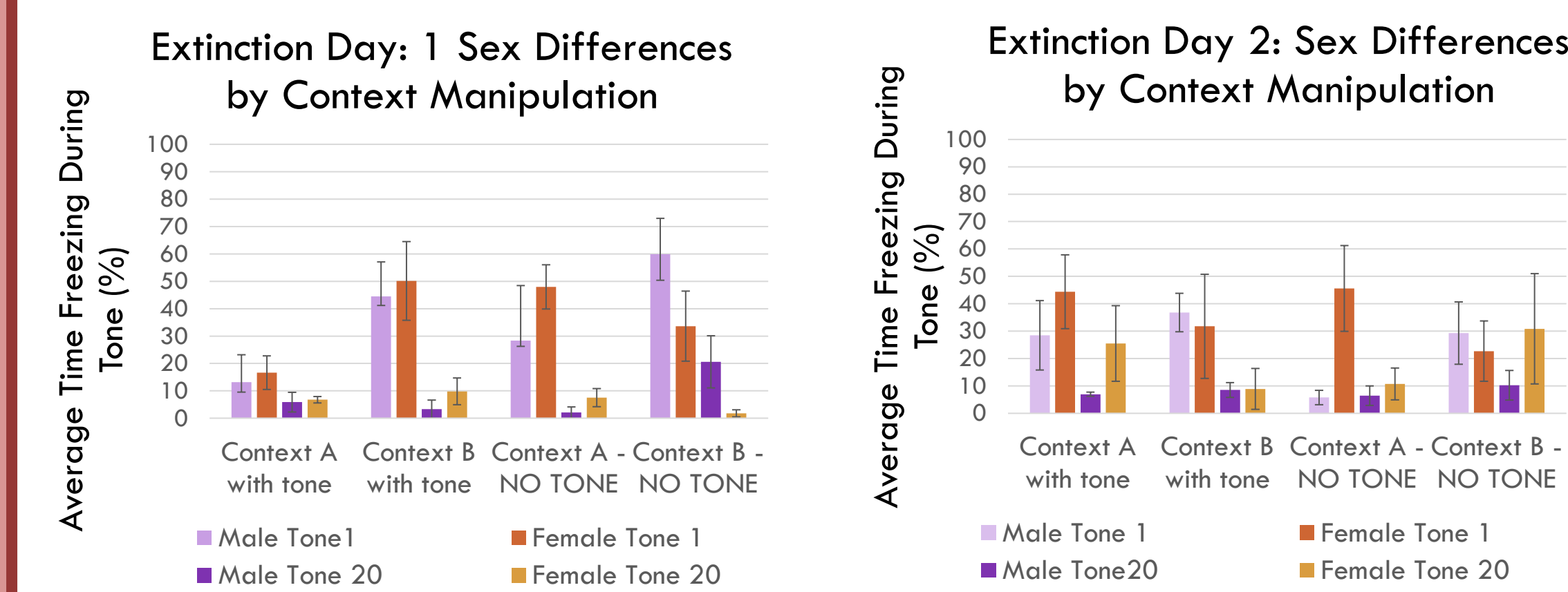
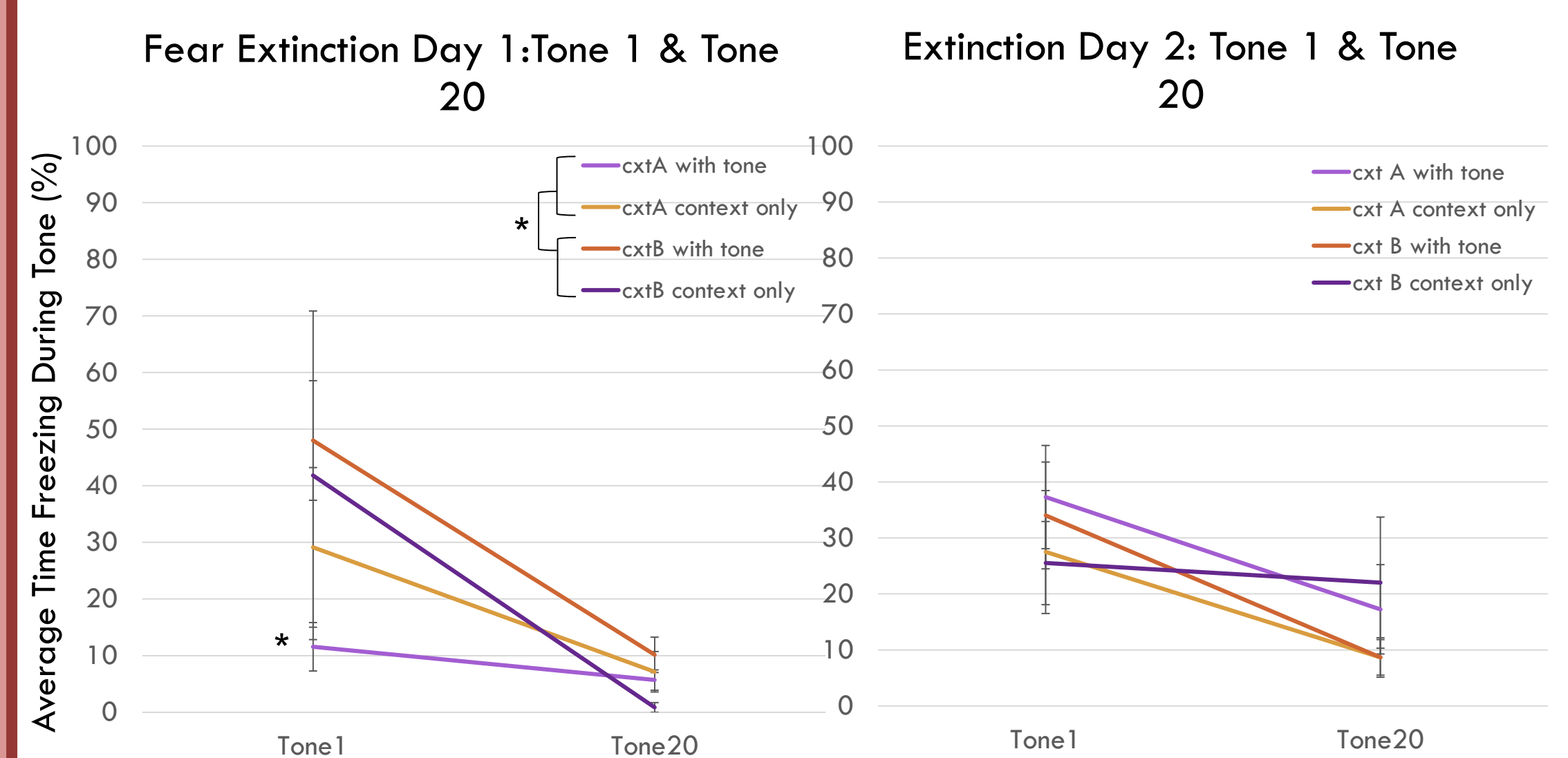
## Results



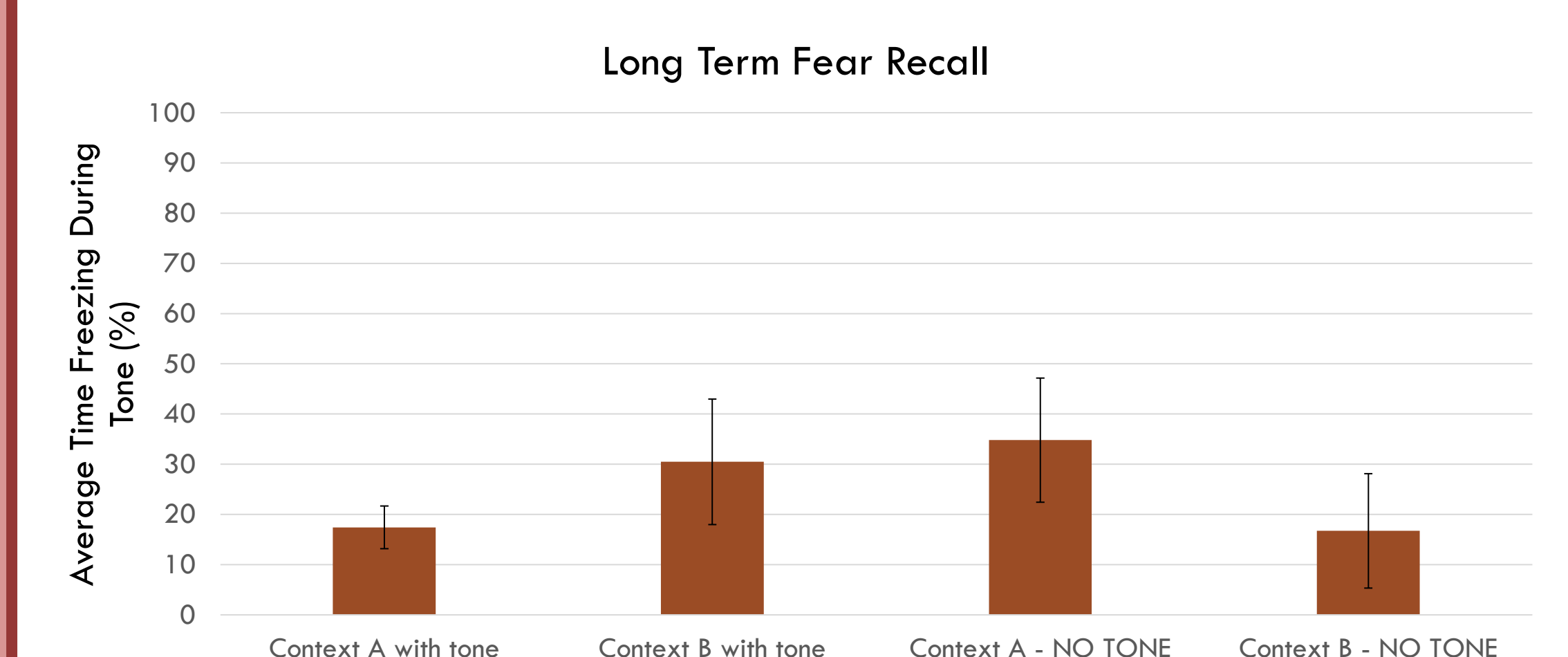
- All mice learned to fear the cue
- Female mice learned faster, but males later caught up ( $p = 0.0325$ )



- Mice froze significantly more during tone, but there was no difference based on context ( $p = 0.003$ )
- There were no difference in freezing between sexes during different retrieval conditions



- During extinction (day 1), freezing differs between groups for tone 1 but not tone 20
- Mice that experienced recall in context A froze less than mice that experienced recall in context B
- Mice that experienced a tone during recall in context A froze less than all other mice.
- There were no significant differences during Extinction day 2



- There were no differences in freezing between the different recall conditions
- The study was not sufficiently powered to determine long term sex differences

## Discussion

- The decreased freezing observed in mice who experienced a tone in the fear conditioning context during retrieval indicates possible value of exposure to an acute fear trigger prior to extinction as a further therapeutic measure.
- The lack of significant sex differences in fear inhibition indicates that during adolescence treatments may not need to be modified based on sex.
- Our results correlate with a previous study<sup>1</sup>, which found that retrieval-extinction manipulation in the training or extinction context weakened fear renewal. However, this study showed that retrieval in the extinction context leads to greater reductions in freezing, while our results showed a greater benefit of retrieval in the training context.
- The study<sup>1</sup> featured retrieval 10 mins prior to extinction, as opposed to our 24-hour spacing; the similarity of the outcomes indicates that timing between exposure to a fear stimulus and extinction therapy is more of a flexible parameter.
- As both studies indicate the benefit of retrieval trials, it would be of value for future experiments to test retrieval trials in both the training and extinction contexts prior to extinction, with variation in the timing between the retrieval and extinction sessions.
- It would also be of value to observe how the time variations impact activity in the basolateral amygdala (BLA) and infralimbic region of the prefrontal cortex (IL).

## References

- (1) Baker, K. D.; McNally, G. P.; Richardson, R. Memory Retrieval before or after Extinction Reduces Recovery of Fear in Adolescent Rats. *Learning & Memory* **2013**, 20 (9), 467–473. <https://doi.org/10.1101/lm.031989.113>.
- (2) Kodak, A.; Fjermestad, K.; Bjelland, I.; Gjestad, R.; Öst, L.-G.; Bjaastad, J. F.; Haugland, B. S. M.; Havik, O. E.; Heiervang, E.; Wergeland, G. J. Long-Term Effectiveness of Cognitive Behavioral Therapy for Youth with Anxiety Disorders. *Journal of Anxiety Disorders* **2018**, 53 (53), 58–67. <https://doi.org/10.1016/j.janxdis.2017.11.003>.

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