

# The effects of trauma on the response to cocaine

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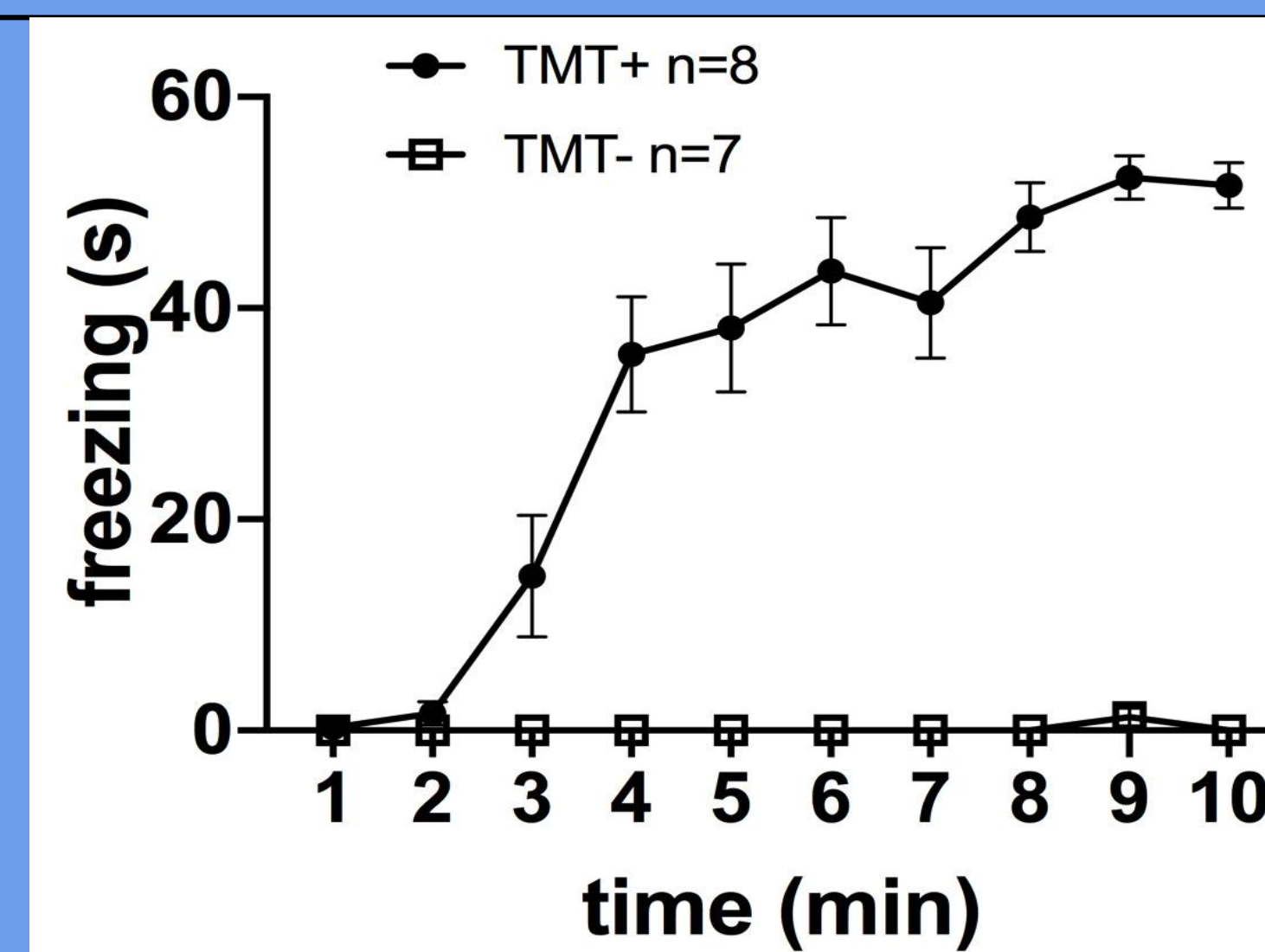
## Background

- Exposure to adverse events is a risk factor for substance use disorder. Stress has been demonstrated to increase cocaine-seeking behaviors.
- We modeled this in an inbred strain of mice by exposing adult males to a predator odor (a synthetic fox pheromone, TMT) and then assessing 1. Cocaine-induced locomotion, and 2. Conditioned place preference (CPP) of cocaine (see Fig. 1).
- TMT resembles predator pheromones, which can cause mice to engage in freezing. Freezing behavior is the absence of any movement, and it is exhibited in order to avoid detection by predators. Since experience with predators is an extremely stressful event for mice, freezing behavior can be used as a measure of stress in a mouse model.
- Cocaine is often associated with increased locomotor activity. Our locomotor assays detect any increases or decreases in locomotor activity. Thus, we expect mice affected by cocaine to display increased locomotor activity when compared to baseline measurements.

## Research Hypotheses

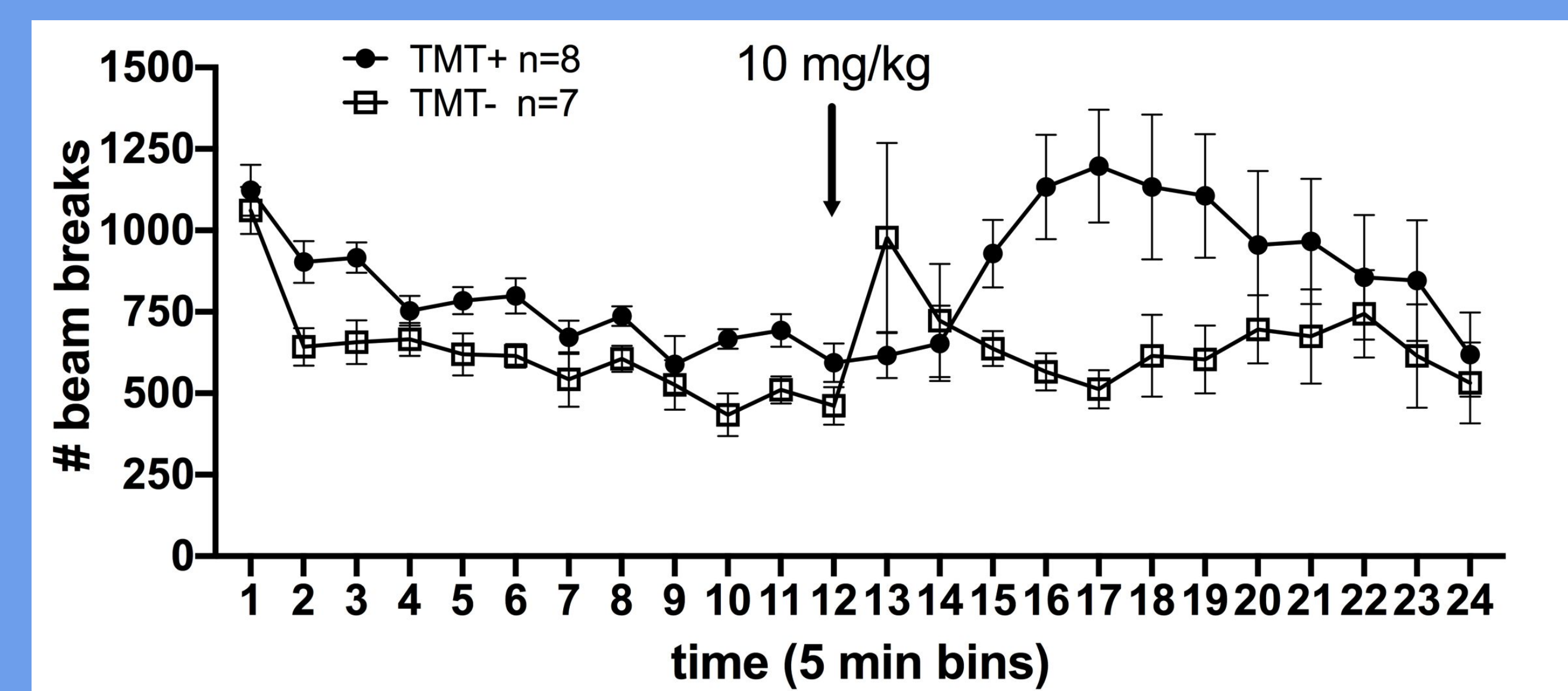
- H1: Adult mice exposed to TMT will display increased freezing behavior during a Conditioned Fear test compared to adult mice not exposed to TMT.
- H2: Adult mice exposed to TMT will display increased locomotor activity compared to adult mice not exposed to TMT.
- H3: Adult mice exposed to TMT will show increased preference for cocaine when compared to adult mice not exposed to TMT.

## Results



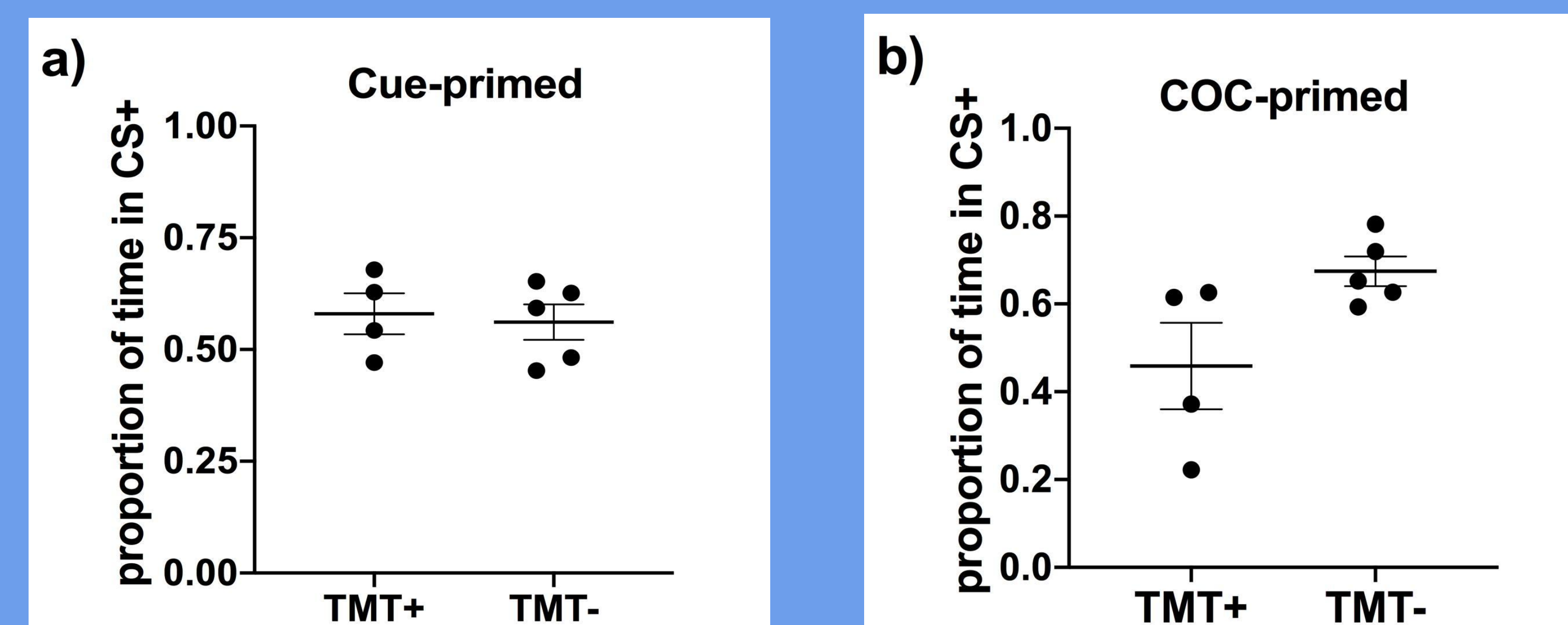
- TMT was an effective stressor as indicated by freezing behavior.

Fig. 2. Across the 10-minute session, TMT-exposed mice (TMT+) froze more than TMT-naive (TMT-) mice, resulting in a significant Time by Group interaction ( $F(9, 117) = 23.07, p < 0.001$ ). A main effect of Time ( $F(3, 42) = 23.74, p < 0.001$ ) and Group ( $F(1, 13) = 219.7, p < 0.0001$ ) was also revealed..



- TMT-exposed mice were more active at baseline (bins 1-12), and had an increased response to a cocaine-challenge (bins 13-24) compared to controls.

Fig. 3. In a 2-hour locomotor test, TMT-exposed (TMT+) mice were more active than non-exposed (TMT-) mice across baseline (bins 1-12) ( $F(1, 13) = 8.4, p = 0.012$ ). Following a cocaine injection (10 mg/kg, i.p.). TMT+ mice showed a cocaine-induced increase in activity, TMT- mice did not ( $F(11, 143) = 3.15, p = 0.008$ ).



- Control mice showed higher cocaine preference when compared to traumatized mice.

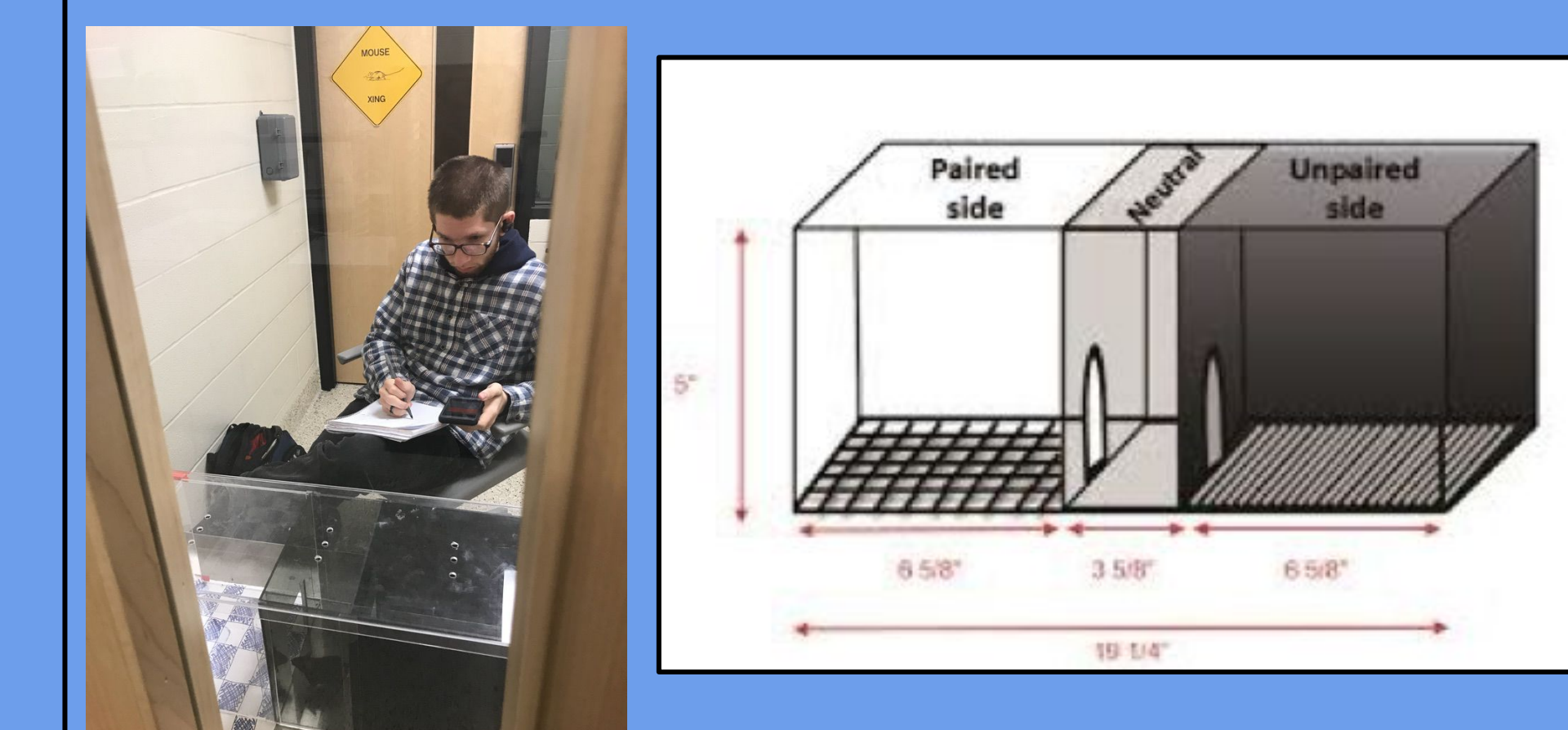
Fig. 4. a) During cue primed testing, no significant differences in cocaine preference were observed between groups ( $p > 0.05$ ) b) During cocaine primed testing, mice not exposed to TMT showed a trend for increased cocaine preference compared to mice that were exposed to TMT ( $t(7) = 2.2, p = 0.056$ ).

## Methods

Sun	Mon	Tue	Wed	Thu	Fri	Sat
Handle (2min/mouse)	PreTest (15min)	CS+ (30min)	CS- (30min)		Cue-primed (15min)	
	CS+ 10mg/kg (30min)	CS- (30min)	CS+ (30min)		Coc-primed (15min)	
					5mg/kg	

- Fig. 1. Schedule of methods for Conditioned Place Preference (CPP). Conditioning occurred with 10 mg/kg of cocaine. Coc-primed testing occurred with 5 mg/kg of cocaine

### Conditioned Place Preference (CPP)



- The CPP consists of three chambers. The two outer chambers differ in the color (e.g. Light or Dark), pattern on the floor (checkerboard or grey), and smell (vanilla or no scent). Subjects are given cocaine injections in only one of the chambers. Thus, cocaine injections become associated with the environmental context in which they were received (known as the CS+). The subject is similarly exposed to the other side of the arena (the unconditioned side known as a CS-) but is given injections of saline. The amount of time spent in the CS+ is used as a measure of cocaine-seeking.

### Locomotor test



- Locomotor activity is tracked using photobeams and recorded by automated computer software.

- Statistical analysis: A two-way ANOVA with TMT exposure (TMT+, TMT-) and Side (CS+, CS-) was run for cue primed and coc-primed testing separately.

## Conclusions

- Traumatized mice showed increased baseline locomotor activity. After cocaine, these mice showed a cocaine-induced spike in locomotion whereas control mice did not show this increase. This suggests that cocaine was more efficacious in TMT+ mice, indicating that trauma could lead to a stronger and more pronounced effect of cocaine.
- No significant differences were observed during cue-primed testing. This may be because the differences between CPP chambers are too subtle to properly condition.
- Interestingly, control mice showed higher cocaine preference when compared to traumatized mice. This lack of preference for the CS+ may be due to the stronger perceived effects of cocaine as suggested by the locomotor data.