

**PAVLOVIAN CONDITIONED FLIGHT RESPONSES IN RATS ARE
GATED BY THREATENING CONTEXTS**

An Undergraduate Research Scholars Thesis

by

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ABSTRACT

Pavlovian Conditioned Flight Responses in Rats are Conditioned by Threatening Contexts

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Humans and animals use environmental cues to determine appropriate defensive responses. Understanding the mechanisms of context-mediated fear responses is crucial, as the dysregulation of these processes are central to trauma and stress-related disorders (such as anxiety or post-traumatic stress disorder). Decades of research establish how context mediates conditioned freezing in rats, but little literature has explained the mechanisms behind flight. To address this, we used a modified Pavlovian conditioning procedure in which the standard conditioned stimulus is replaced by a serial-compound stimulus (SCS) comprised of a pure tone followed by white noise. Rodents display freezing to the tone and flight to the white noise in this paradigm. Interestingly, flight is only observed in the conditioning context. Here, we conducted two experiments to further investigate how flight responses are contextually gated. 1) Conditioned animals were placed into a novel context where one group of animals received unsigned footshocks (Shock) and one group did not receive footshocks (No-Shock). The next day both groups were returned to this context and underwent SCS-alone presentations. Animals that received unsigned footshock displayed robust flight responses, whereas No-Shock animals did not. 2) Conditioned animals either underwent fear extinction of the conditioning context by

exposing the rats to the context for 45 min (Ext) or were exposed to a novel context for the same period of time (No Ext). The next day both groups were presented SCS-alone trials in the conditioning context. No-Ext rats still displayed robust flight responses to the SCS, whereas Ext animals did not. Collectively, these two results demonstrate that the contextual gating of flight behavior in rats is driven by context fear and suggest that flight is driven by a high fear state combining auditory and environmental fear. Understanding how context regulates fear responses is vital to improving current trauma and stress-related therapies.

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NOMENCLATURE

PTSD	Post-traumatic stress disorder
SCS	Serial-compound stimulus
Shock	Rodents that received a trial of un-sigaled foot-shock following conditioning trials
No-Shock	Rodents that were placed in the same context as Shock animals, but did not receive a trial of un-sigaled foot shock following conditioning trials
Ext	Rodents that extinguished the conditioning context before returning to the context
No-Ext	Rodents that did not extinguish the conditioning context before returning to the context
CS	Conditioned stimulus
US	Unconditioned stimulus

CHAPTER I

INTRODUCTION

Individuals that endure traumatic events, such as combat or sexual abuse, can develop anxiety and trauma-related disorders such as anxiety, panic disorder, or post-traumatic disorder (PTSD) (Liberzon and Sripada 2008). PTSD is commonly characterized by heightened fear and anxiety to otherwise harmless stimuli (e.g. a car backfiring) that trigger the recall of traumatic memories (e.g. gunshots). Associations between salient stimuli and traumatic events occurs due to learning and memory processes which can be modeled using rodents. For example, aversive learning and memory is commonly studied using Pavlovian conditioning paradigms in which animals learn that an innocuous stimulus, such an auditory tone, is paired with an aversive outcome, such as a mild footshock. Over repeated presentations, the previously innocuous tone becomes a fearful conditioned stimulus (CS) which predicts the aversive footshock, an unconditioned stimulus (US). Rodents will also show conditioned fear to the context in which they were shocked (Fanselow, 1980). Fear in rodents has traditionally been measured in terms of immobility, or time spent freezing, which is an evolutionarily conserved defensive behavior to prevent detection by predators. Animals and humans alike use environmental cues to determine the most appropriate defensive response in the face of danger. For instance, if a car is speeding towards you while you are in the middle of the street, freezing in place would be a poor response in comparison to quickly running towards the sidewalk. Conversely, if you are standing on the sidewalk then it would be wise to stay in place where you are safe. The processing of contextual information is critical for regulating fear and anxiety, and indeed, the dysregulation of contextual processing appears to be central to PTSD (Garfinkel et al. 2014; Liberzon and Sripada 2008).

Contexts can broadly be defined as internal (e.g., hormone levels, time) or external (e.g., background stimuli) settings of which animals use to form emotional memories as well as expectations of similar circumstances (Maren et al. 2013). Contexts are also vital to the retrieval of memories, which allows animals to adapt their defensive response depending on their environmental context. Animals use contextual information to assign salience to discrete cues, such as CSs and USs within Pavlovian fear conditioning. One example by which context regulates fear is the context specificity of extinction learning. Fear extinction is an inhibitory learning process by which animals come to learn that a CS no longer predicts the US by presenting the CS numerous times and omitting the US (Bouton 2004). If the animal is presented the CS in the same extinction context the next day it will show low levels of fear, however, CS presentation in any other context will cause a relapse of fear. This phenomenon is known as renewal (Vervliet et al. 2013). In another phenomenon known as reinstatement, presentation of an unpaired US within the extinction context will drive the relapse of fear to a previously extinguished CS. (Goode and Maren 2014). Both renewal and reinstatement are well studied processes by which researchers have sought to understand how contextual information mediates aversive memories that have led to substantial advancements in the field of learning and memory. However, this advancement is limited by behavior paradigms which only produce passive freezing responses as behavioral correlates of fear expression.

Although fear is traditionally measured in terms of freezing, animals have a variety of other fear responses, such as darting, fighting, and flight (Blanchard and Blanchard 2008). Despite the decades of work on understanding the contextual regulation of freezing responses, contextual mediation of conditioned flight behavior is not understood. A modified Pavlovian conditioning paradigm was created to study both passive and active behaviors, by using a serial-

compound stimulus (SCS), composed of a pure tone followed by white noise in place of the standard CS. In the original paper, Fadok and colleagues (2017) found that the SCS produced rapid switching between freezing and flight behaviors, specifically that mice froze to the pure tone and displayed flight behaviors to white noise (Fadok et al., 2017). Interestingly, flight behavior was only observed in the conditioning context (Fadok et al. 2017). Here, we hypothesized that contextual fear generates a high fear state driving flight behavior in rodents. In this study, we replicated and extended Fadok et al.'s (2017) results in a sample of rats. We found that rats exhibit similar flight responses to mice, and, in line with our hypothesis, flight behavior could be both driven to other threatening contexts and blocked within the conditioning context by extinguishing contextual fear. This paradigm represents a unique opportunity to not only study passive and active fear responses, but also the context dependency of conditioned flight responses.

CHAPTER II

METHODS

Subjects

In this study, a total of 8 female and 8 male adult Wistar rats (Wistar Hannover, ~200g) bred in-house, and 24 female and 24 male Long-Evans rats (Blue Spruce, ~200g) obtained via a commercial supplier (Envigo, Indianapolis, IN), were used. All rats were individually housed in cages, kept on a structured light/dark schedule (14:10 light/dark cycle), and had no feeding restrictions. Each animal was handled for approximately one minute each day, for five days before the experiment to familiarize them to the experimenters. Experiments were conducted at the same time every day, during the light phase. All experiments followed guidelines and regulations imposed by the Institutional Animal Care and Use Committee at Texas A&M University.

Behavioral apparatus and procedure

All behavioral experiments were conducted in one of two rooms, each of which contained eight rodent conditioning chambers (30 x 24 x 21 cm; Med Associates, St. Albans, VT). Each conditioning chamber consisted of two aluminum sides, a Plexiglass back wall, ceiling, and door. The floor consisted of a grid of 19 steel rods (4mm diameter) evenly spaced apart from each other (1.5cm), that were connected to a shock source and solid-state grid scrambler (Med Associates) to generate the electric footshocks. Inside each conditioning chamber was a speaker mounted to the side of one of the aluminum walls to emit auditory stimuli for the experiments (pure tone, white noise). Different contexts were created by using different combinations of visual, tactile, auditory, and olfactory stimuli. For example, context A (always used as the

habituation context) was comprised of white ambient lighting, cage lights turned off, conditioning chamber doors were left open, black plastic floors were placed over the shock grid, fans were turned on for ambient background noise, and the chambers were wiped down with a 3% acetic acid solution. For context B (always used as the conditioning context), was comprised of red ambient lighting, cage lights on, conditioning chamber doors were closed, no plastic floor was used, fans were turned off, and all chambers were wiped down with a 1% ammonium solution. Finally, context C (used for the unsignaled footshock context) was comprised of white ambient lighting, cage lights off, conditioning chambers were closed, no plastic floor was used, fans were turned on, and chambers were wiped down with a 70% ethanol solution. Locomotion in rats was determined through the displacements of the conditioning chamber onto the load cell beneath it. Displacements of the chamber from locomotor activity generate a voltage in the load cell, which are interpreted as an indirect metric of motion. Freezing, however, is interpreted whenever there is an absence of motion or the locomotion that exists occurs under threshold (of 10 a.u.) for at least one second. Freezing measurements during conditioning trials were averaged across trials per day. Freezing and motion data were measured during baseline periods and SCS presentations in all studies conducted. Flight scores were calculated using motion data from each SCS trial as: $[(\text{Noise} - \text{Tone}) / (\text{Noise} + \text{Tone})]$. For each experiment, the SCS consisted of 10s of pure tone (7 kHz, 80 dBs) pips (500ms, 1 Hz) immediately followed by 10s of white noise pips (1-20 kHz, 80 dBs).

For the first experiment, the behavioral paradigm consisted of habituation to the SCS, fear conditioning, and a retrieval test. Each group consisted of 4 females and 4 males ($n=8$). Habituation took place in context A and consisted of a 3-minute baseline period before 4 SCS-alone presentations with 60s inter-stimulus intervals (ISI). Fear conditioning took place three

consecutive days in context B and consisted of a 3 min baseline period followed by five SCS-US (2sec, 1mA) pairings (60s ISI). On the final day, all rats were presented four SCS-alone trials in either the habituation context (context A) or the conditioning context (context B).

For the second experiment, the behavioral paradigm consisted of habituation to the SCS, fear conditioning, un-signaled footshock trials, followed by a final retrieval test day (Fig. 2A). Each group consisted of 4 females and 4 males ($n=8$). Habituation (context A) and fear conditioning (context B) procedures were replicated from the previous experiment. Following conditioning both groups of rats were placed into a third, novel context (context C) and consisted of a 3 minute baseline period followed by five trials of footshocks (2sec, 1mA) without preceding presentations of the SCS in one group of rats (Shock), while the other group was exposed to the same context for the same amount of time without footshocks (No-Shock), both with 60sec ISIs. The final retrieval day both groups of animals were returned to the same context (context C) and played four SCS-alone trials (60sec ISI).

The final experiment conducted, referred to as the context extinction experiment, the behavioral paradigm consisted of habituation, fear conditioning, a context extinction trial, followed by a final retrieval test. Each group consisted of 4 females and 4 males ($n=8$). Habituation (context A) and fear conditioning (context B) procedures were replicated from the last two experiments. Following conditioning, one group was returned to the conditioning context (Ext, context B) to extinguish fear to the conditioning context, while the other group was returned to the habituation context (No-Ext, context A). Both groups were exposed to their contexts for 45 minutes. The next day, both groups were returned to the conditioning (context B) context and played four SCS-alone trials (60sec ISI).

Data analysis

All data were analyzed with analysis of variance (ANOVA) with the variables: group, trials, and sex for conditioning, extinction, and retrieval trials across all experiments. All data are represented as means \pm s.e.m.

CHAPTER III

RESULTS

Wistar pilot

To determine if flight behavior is context dependent and if it could be replicated in rats, we ran an experiment in which flight was compared following fear conditioning between the group of animals returned to a neutral context and those returned to a threatening context (Fig. 1A). During habituation, rats showed no fear to either the pure tone or white noise [main effect of trials: $F(3,36) = .515, p = .6748$; main effect of stimulus: $F(1,12) = .197, p = .6649$]. Both groups showed increased freezing throughout fear conditioning [main effect of days: $F(2,28) = 10.523, p < .05$], and levels of freezing did not differ between groups [days x group interaction: $F(2,28) = 1.197, p = .3170$] (Fig. 1C). Importantly, rats froze at a high rate to the pure tone presentation of the SCS, but unfroze once white noise was presented [main effect of SCS stimulus: $F(4,48) = 162.749, p < .0001$]. This is nearly identical to the findings of Fadok et al. (2017) and demonstrate that rats also display robust flight responses to white noise this paradigm.

To test if flight responses in rats are also context-dependent, we next presented rats with four SCS-alone presentations in either the habituation or conditioning contexts. As seen here (Fig. 1B), Wistar rats have previously been shown to exhibit low levels of context freezing (Pomrenze et al. 2019), which creates a low ceiling for discriminating context fear. Indeed, rats returned to the conditioning context showed higher levels of freezing during the baseline period which trended toward, but just missed, statistical significance [main effect of group: $F(1,12) = 3.469, p = .0872$]. Despite this, during the first SCS presentation, there was no overall difference

in the total amount of freezing during the SCS [main effect of group: $F(1,12) = 3.958, p = .0699$], but rats in the conditioning context showed the same switch from freezing to flight as in conditioning, whereas rats in the habituation context actually showed an increase in freezing in response to the white noise [SCS stimulus x group interaction: $F(1,12) = 12.841, p = .0038$] (Fig. 1D).

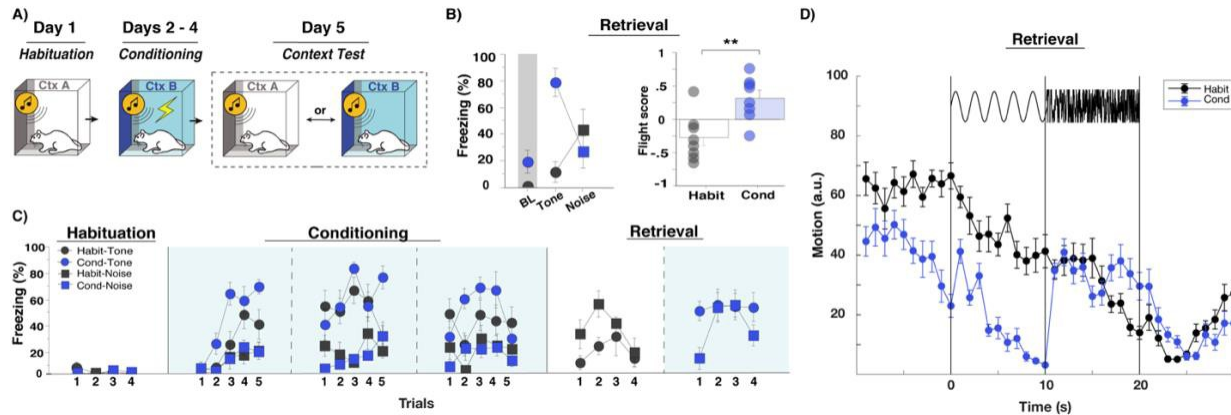


Figure 1. **A)** Behavioral protocol for the Wistar pilot experiment. Animals were either returned to the habituation ($n = 8$) or conditioning ($n = 8$) contexts for retrieval testing. **B)** Freezing levels during the first SCS trial of the retrieval day of both groups of animals, showing a switch from freezing to flight to white noise presentations in the group tested in a threatening context. Followed by a flight ratio pilot from the retrieval day of training. **C)** Freezing data across behavioral testing. Flight behavior to white noise develops as early as the end of the first day of conditioning. **D)** An example of raw motion plotted per second of the first SCS trial from the retrieval day. The blue curve representing the sharp increase in motion to the white noise within the group tested in the conditioning context, while the group tested in the habituation context showed a continual decrease in motion across time. ** represents $p < .01$.

Unsignaled footshock

To determine how flight responses are contextually gated, we next sought to determine if flight responses could be driven in threatening environments other than the conditioning context by presenting SCS-alone trials to conditioned animals in an environment they were previously shocked in but was not associated with the SCS (Fig. 2A). During habituation and conditioning, rats once again showed no initial fear to either the tone or white noise during habituation [main

effect of trials: $F(3,33) = 1.543, p = .221$;, main effect of stimulus: $F(1,11) = 2.904, p = .1164$], acquired fear to the SCS during conditioning with no differences across groups [main effect of days: $F(2,26) = 52.670, p < .0001$; days x group interaction: $F(2,26) = .254, p = .7779$], and showed robust flight responses to white noise by the end of conditioning [main effect of stimulus: $F(1,13) = 113.469, p < .0001$]. Following conditioning, the group of rats that received unsignaled footshocks (Shock) showed reliable increased levels of freezing as trials continued, while rats merely exposed to context C maintained low levels of freezing (No-Shock), as shown in Fig. 2B [main effect of group: $F(1,27) = 92.704, p < .0001$; main effect of trials: $F(5,135) = 11.797, p < .0001$; trials x group interaction: $F(5,135) = 12.010, p < .0001$]. For retrieval testing, Shock animals showed high levels of context fear via baseline freezing, whereas No-Shock animals showed very little [main effect of group: $F(1,27) = 238.363, p < .0001$]. During the first SCS trial, Shock animals showed a robust switch from freezing to flight as indicated by a high flight score [main effect of group: $F(1,28) = 26.962, p < .0001$]. Although Shock animals showed overall higher amounts of freezing, driven by high amounts of freezing to the pure tone [main effect of group: $F(1,27) = 5.845, p = .0226$], Shock animals showed a decrease in freezing once the white noise was presented, whereas No-Shock animals actually showed higher freezing to the white noise [trials x group interaction: $F(1,27) = 10.280, p = .0034$]. This is similar to the results of the previous experiment and suggests that flight behavior in rats is gated by threatening contexts.

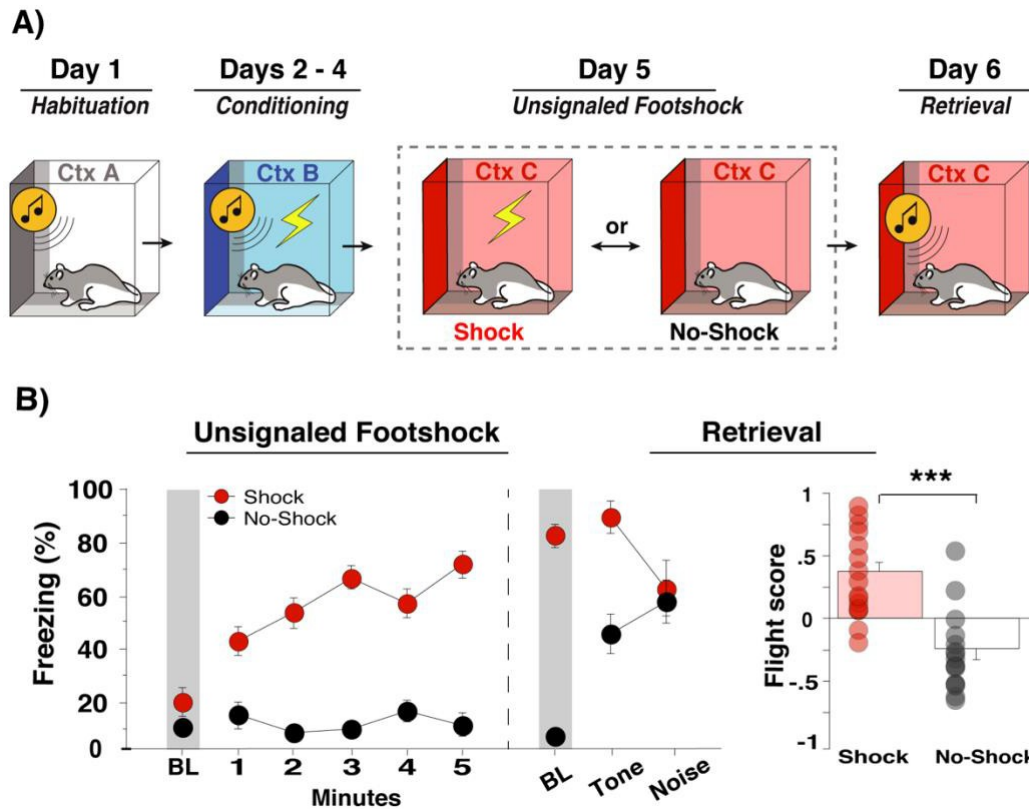


Figure 2. **A)** Behavioral protocol for the un-signaled footshock experiment. One group of animals received un-signaled footshock ($n = 16$) while the other group did not ($n = 16$) before returning to the third, novel context. **B)** First plot shows freezing levels of both groups during the unsignaled footshock trials. Shock animals showed a steady increase as trials proceeded. Shock animals exhibited high baseline freezing during retrieval testing and increased flight compared to No-shock animals, as shown by freezing and flight score data. *** represents $p < .001$.

Context extinction

By the same logic as the previous experiment, if conditioned flight behaviors in rats are gated by fear to threatening contexts, then we predict that extinguished fear to the conditioning context will block flight responses within that context. During habituation and conditioning, rats showed no initial fear to either the tone or white noise during habituation [main effect of trials: $F(3,84) = .587, p = .6255$; main effect of stimulus: $F(1,28) = 2.002, p = .1681$], acquired fear to the SCS during conditioning with no differences across groups [main effect of days: $F(2,56) = 73.610, p < .0001$; days x group interaction: $F(2,56) = .148, p = .8629$], and showed robust flight responses to white noise by the end of conditioning trials [main effect of stimulus: $F(1,28) =$

144.857, $p < .0001$]. Groups of rats were returned in either the habituation or conditioning context following fear conditioning (Fig. 3A). Both groups were exposed to the context for 45 minutes, the group exposed to the conditioning context extinguished fear to the threatening context (Ext), as reflected in the decreased freezing levels over time, whereas the group exposed to the habituation context did not extinguish (No-Ext) [group x trial interaction: $F(7,84) = 2.837, p < .05$] (Fig 3B). The following day when both groups were returned to the conditioning context, Ext animals showed reduced freezing to baseline which trended towards, but just missed, statistical significance [main effect of group: $F(1,12) = 3.257, p = .0963$]. In line with this, Ext animals showed lower levels of flight compared to the No-Ext animals which also trended towards but missed significance [main effect of group: $F(1,12) = 3.714, p = .0780$] (Fig. 3B). Although the differences between Ext and No-Ext animals were not significant, the results trend in the same direction as our proposed hypothesis. It appears that Ext animals only partially extinguished fear to the conditioning context, and thus, still showed residual context fear. With this in mind, our findings still support the hypothesis that context fear drives flight behavior in rats.

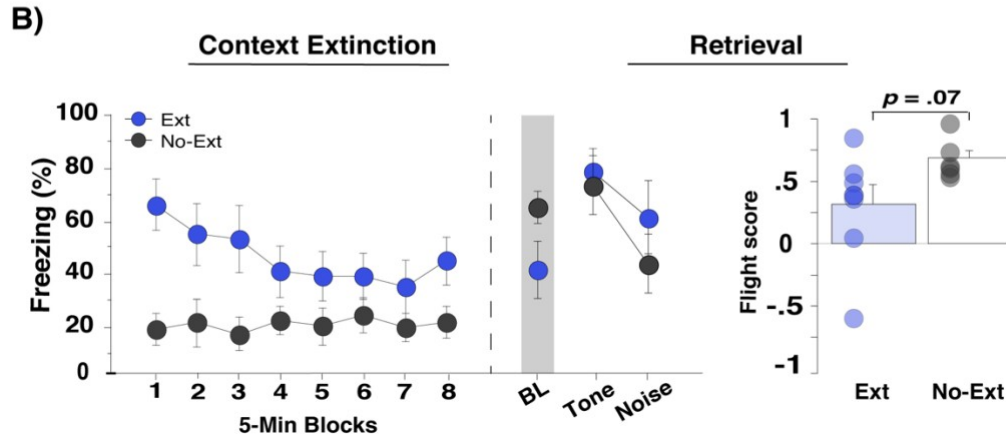
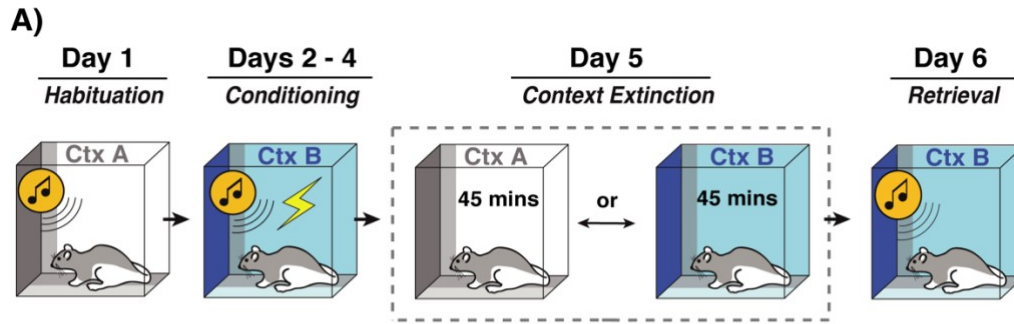


Figure 3. **A)** Behavioral protocol for the context extinction experiment. One group of animals received extinguished conditioning context fear (Ext, $n = 8$) while the other group did not (No-Ext, $n = 8$) before returning to the conditioning context. **B)** Ext animals showed decreases in freezing as context extinction proceeded. When the animals were brought back to this context 24 hours later for retrieval testing, Ext animals showed reduced freezing, but unfortunately still showed relatively high levels of context fear. In line with this, as shown by freezing and flight score data, both Ext and No-Ext groups showed increased flight in response to white noise presentations. However, Ext animals showed a trend towards reduced flight compared to No-Ext animals.

CHAPTER IV

DISCUSSION

The current study sought to replicate and extend previous work on active fear responses in rats, and more specifically, the contextual regulation of these responses. Previously, Fadok et al. (2017) developed a novel Pavlovian conditioning paradigm in which an SCS drove both conditioned freezing and flight behavior in mice, and interestingly, flight behavior was only observed in the original conditioning context. We here replicated these findings in rats and further show that conditioned flight behavior is gated by context fear. We found that flight behavior could be driven to an SCS in other shock-associate contexts besides the conditioning context, and that extinguishing fear to the conditioned context suppressed flight. This further validates the use of the SCS paradigm to investigate the contextual regulation of active fear behavior.

One limitation to consider within our study is the difference in methods of measuring movement between our study and those used by Fadok and colleagues (2017). In the original paper by Fadok and colleagues, flight behavior was quantified using direct measurements of speed through the use of cameras and via jumping behavior, whereas we used an indirect measure of motion recorded via a loadcell and did not quantify jumping or other escape-like behaviors. Although rats do exhibit escape-like behavior such as jumping that is specific to white noise, it is seldom in nature (unpublished results). Despite these limitations, the increase in movement upon noise presentations, and its context specificity, is consistent to the findings of Fadok et al. (2017). One possibility to explain why rats do not show escape-like behaviors to the same extent of mice may be due to the relatively small conditioning chambers, compared to the

relatively larger chambers that mice are tested in. Larger conditioning chambers would allow the rats more room to exhibit active defensive responses such as jumping or darting behavior. This has not yet been tested and would be a good avenue for future investigations. Additionally, one of the major limitations of this study is that rats did not fully extinguish fear to the conditioning context in the third experiment, which resulted in residual context fear. Despite only partially extinguishing context fear, we still saw a trend towards diminished flight responses which is in line with our other data suggesting that contextual fear gates flight responses. It is not surprising that a single day of extinction training was insufficient to fully extinguish context fear when conditioning occurred over 3 consecutive days. We expect that fully extinguishing context fear would have completely blocked flight within the conditioning context.

In this study, we determined that contextual fear drives flight behavior, however, we only tested contextual fear through shock-associated contexts. Fear can also be driven to contexts by the use of innately aversive olfactory stimuli, such as trimethyl-thiazoline (TMT), a fox scent. Innately aversive or attractive scents can gate between attractive or aversive behaviors in animals (Li and Liberles 2015). Rats show fear to innately aversive predatory odors via a multitude of defensive behaviors, including both freezing and avoidance (Rosen et al., 2015). It is important to understand how associative learning influences flight behavior, as the interaction of associative learning and olfactory-mediated behaviors can block panic-like responses in animals, due to anticipatory stress (Mongeau et al. 2003). With these findings in mind, we would not expect flight responses to the SCS stimuli in a context with an innately aversive scent, like TMT, as these findings suggest that flight responses are specific to shock-associated contexts. Future work should take this opportunity to determine if playing the SCS in a context with an innately aversive scent would evoke the same flight responses that arise from shock-associated contexts,

to ultimately understand the competitive nature of behaviors that arise from associate learning and olfactory stimuli.

In conclusion, our findings support the model of aversive learning and memory studying a novel conditioned fear response. This is consistent with prior work on flight behavior using a novel Pavlovian paradigm and is important because it provides further evidence that flight behavior is generated by high fear states from context fear, and that extinction of context fear in turn suppresses these behaviors in rats. Our results demonstrate that this paradigm is useful for studying the contextual regulation of active fear responses and the neural circuits that govern it. In the original paper by Fadok and colleagues, they determined that neurons expressing corticotropin-releasing hormone (CRH+) in the central amygdala (CeA) plays a role in gating flight behavior in mice. Moreover, it is well known that both the hippocampus (Maren et al., 2013) and bed nucleus of the stria terminalis (Good and Maren, 2014) play critical roles in the expression of context fear, and thus, represent likely targets for the mediating of contextually gated flight responses. Better understanding the role of these neural circuits in flight behavior is critical to advance not only behavioral, but also pharmacological treatments for stress and trauma-related disorders.

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