

**BEHAVIORAL FACTORS GOVERNING THE EXTINCTION OF  
AMBIGUOUS THREAT CUES**

An Undergraduate Research Scholars Thesis

by

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## **ABSTRACT**

### **Behavioral Factors Governing the Extinction of Ambiguous Threat Cues**

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The purpose of this experiment was to examine the cognitive mechanisms by which an animal uses associations to learn about temporally ambiguous aversive events. Traditionally, associative learning using forwards conditioning, where a conditioned stimulus (CS) presentation precedes the delivery of an unconditioned stimulus (US), and thus responses to the CS following conditioning can be attributed to the predictive value that the CS acquires. However, studies have also shown that animals acquire conditioning responses (CR) in a backwards fashion (US → CS), despite the lack of temporal information that the stimulus provides about the US (Heth 1976; Ayres et al., 1987). To examine this, in a 64-rodent study, animals were conditioned to either a forward (temporally predictable) or backward (temporally unpredictable) conditioned stimulus (CS). Following conditioning, animals were given extinction training in which they experienced repeated presentations of the CS in the absence of the US. On the final day of the experiment, the animals were returned to the original context to test whether fear to the context would be attenuated by a preceding reduction of fear to the tone. We hypothesized that the relationship between the shock stimulus and cognizance of the conditioning context will be mediated by the unpredictable tone. Analogously, the results indicated that extinguishing fear to the conditioned tone will attenuate fear to the global context fear during retrieval.

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## NOMENCLATURE

BW	Backwards
FW	Forward
CS	Conditioned Stimulus
US	Unconditioned stimulus
CR	Conditioned response
Ext	Extinction
NoExt	No extinction

# CHAPTER I

## INTRODUCTION

An animal uses associations between environmental cues and aversive events to prepare for or avoid potentially harmful stimuli. In the laboratory, Pavlovian fear conditioning is a behavioral paradigm for understanding the cognitive mechanisms that drive learning about aversive events (Maren 2001; Maren et al. 2013). In a standard fear conditioning procedure, an animal (rat) is exposed to repeated presentations of an initially innocuous cue (conditioned stimulus, CS) immediately followed by an aversive event (unconditioned stimulus, US) that triggers an immediate fear based unconditioned response (UR). After multiple trials, a conditioned response (CR) occurs following presentation of the CS alone (Pavlov 1927). In Pavlovian conditioning in rodents, a CR consists of a freezing response that is an innate, behavioral defense mechanism that occurs in response to the activation of the fear system (Fanselow 2005). In regards to freezing behavior elicited by a CS, the rat will use this defense mechanism if it has learned the association between the CS and the onset of an unavoidable US. In other words, rats will freeze to CS presentation if the CS has been previously conditioned to predict the onset of the US, but rats will not freeze to an unconditioned innocuous CS because it is not associated with the onset of a fear eliciting event. These freezing responses are analogous with those triggered by the aversive US, however CS elicited behavioral (i.e. freezing) and physiological (i.e. increased heart rate) changes appear to allow the animals to prepare for or altogether avoid the onset of an aversive US (Fanselow 1984; Ledoux et al. 1998; Fanselow 2005). Thus, freezing behavior elicited by a conditioned CS is an adaptive response in that it permits an animal to prepare for an incoming threat.

The intensity of the CS elicited CR is an outcome of the CS-US association and is therefore able to be influenced by new information. For example, in addition to acquiring freezing responses to a CS through fear conditioning, animals can also learn that the CS no longer signals the onset of a threat cue via extinction training, where the relationship between the CS and US is degraded by presenting the CS alone many times without the aversive US (Pavlov 1927). After repeated presentations, CS conditioned fear responses (i.e. freezing) are attenuated by reinforcement of the CS without the occurrence of the US (Chang et al., 2009; Myers & Davis 2002; Pavlov 1927). In other words, an animal can use extinction training to learn that the CS is no longer predictive of the onset of the US. The ability to extinguish fear to specific stimuli is adaptive in that it allows an organism to update contingencies between environmental cues and aversive events. In the present experiment, we used CS extinction training to determine the meditative effects of an extinguished CS on fear to a conditioning context.

Although Pavlovian conditioning has been fundamental in our understanding of the mechanisms by which an organism learns associations between stimuli and aversive events, these experiments are typically conducted in a forward fashion. During forward conditioning, a direct CS-US association occurs due to the temporal predictability of the US (Rescorla & Wagner 1972). Thus, freezing responses to a CS following forward conditioning can be attributed to the predictive value that the CS acquires after conditioning. For example, a combat veteran may find that the sound of an exploding firework resembles the firing of a gun, which may have a direct relationship with an aversive event such as an injured comrade. However, it is not always the case that a threat cue is temporally predictable. For example, the same veteran may notice that the smell of diesel fuel triggers a similar fear response to the those elicited by firework sounds. Although the smell may not be directly related to the onset of any particular aversive memory, it is indirectly

associated with the aversive event through a retrieval of the context (i.e. memories of base camp). Along these same lines, in the laboratory, studies have shown that animals acquire conditioned responses to sensory stimuli conditioned in a backward fashion, in which the aversive CS presentation always follows the US, despite the lack of temporal information that the sensory stimulus provides about the US (Heth 1976; Ayres et al. 1987; Cole & Miller 1999). Although the CS does not predict the onset of an aversive US, during the early trials of a backwards conditioning procedure, the fear response (i.e. freezing) elicited by a backwards conditioned CS may suggest that backwards CS presentation allows the animal to recall the physical context where the aversive event occurred, consequently triggering a freezing response to the CS (Cole & Miller 1999). Thus, the way an animal uses environmental cues to resolve an aversive US may be dependent on whether the threat cue is temporally predictable or unpredictable. In other words, the cognitive mechanisms by which an animal acquires information about a temporally ambiguous threat cue may be the result of an indirect relationship between the CS and the aversive US via the physical context, where a forwards conditioned CS has acquired predictive value to detect the onset of the aversive US due to the temporal arrangement of the stimuli. Because of this, there is tremendous clinical value in understanding how animals learn about environmental cues that do not directly signal the onset of an aversive event.

The present study aims to understand the cognitive mechanisms by which an animal resolves a temporally ambiguous threat cue by using a backwards conditioning paradigm. Previous work in our laboratory has demonstrated that fear to a backwards trained CS is mediated by fear to the physical context in which the conditioning took place (unpublished observations). For this study, animals were first conditioned to either a forward (CS-US) or backward (US-CS) pairing of stimuli. The following two days, one group of animals from each of the forward and backwards



trained groups was returned to the original conditioning context while another group from each forwards and backwards trained groups was exposed to a novel context for an equivalent amount of time. On the testing day, all animals were placed into a novel context and given 12 CS presentations to examine whether or not extinction of the original conditioning context reduced fear to the auditory CS. Consistent with our hypothesis, animals that were trained to a backward (but not forward) CS and were extinguished in the original conditioning context experienced a consequential reduction of fear to the CS. Furthermore, these data provide more evidence supporting the theory that the CS forms an indirect association with the US during backwards conditioning trials through an association with the physical context (Cole & Miller 1999).

As a follow up to the previous study, the goal of the present experiment was to examine if the opposite is true. That is, rather than context extinction training, rats instead experienced tone extinction training and fear to the original conditioning context was examined. We hypothesized that the study would indicate that extinction of fear to a backward (but not forward) trained CS would subsequently reduce fear to the conditioning context where the aversive event took place.

To test our hypothesis, animals were first conditioned to either a forward (CS-US) or a backward (US-CS) stimulus. On the following two days, animals from each backwards and forwards trained groups underwent tone extinction in which they received 45 CS presentations in the absence of the US. In addition, a separate group of forward and backward conditioned rats were exposed to the same context for an equivalent amount of time however did not receive any CS presentations. This created four experimental groups; forward conditioned rats that received tone extinction training (FW-Ext), forward conditioned groups that did not receive extinction training (FW-NoExt), backwards conditioned rats that received tone extinction training (BW-Ext), and backwards conditioned rats that did not receive tone extinction training (BW-NoExt). On the

last day, animals underwent retrieval sessions where animals were returned to the conditioning context for a period of time with no presentation of the CS or the US and levels of freezing were recorded for all sessions and compared for analysis.

## **CHAPTER II**

### **METHODS**

#### **Subjects**

Sixty-four experimentally naive, male, Long-Evans derived (Blue-Spruce) rats (200-250g) from Harlan Laboratory served as subjects. Subjects were individually housed in climate-controlled vivarium with food and water accessible ad libitum. The rats were kept on a 14:10 hour light: dark cycle. The rats were handled for approximately one minute each day for three days prior to the experiment. All parts of the experiment including the rodents were conducted under supervision of experienced researchers at Texas A&M University, and followed state and federal regulatory guidance applicable to the humane and ethical conduct of such research with Texas A&M University IACUC approval.

#### **Apparatus**

For all behavioral sessions, sixteen identical rodent conditioning chambers (21 cm) located in two rooms (Room 1 and Room 2, eight chambers per room) were used. Each conditioning chamber consisted of a conditioning box that rested on a load-cell platform inside a beige cabinet with hinged doors. A camera is attached to the ceiling of the cabinet for monitoring the movement of rats during the sessions. The cage was made of two aluminum sidewalls, clear Plexiglas rear wall and ceiling, clear Plexiglas hinged doors, and grid floors consisting of 19 stainless steel rods connected to a shock source for delivery of the US (2 seconds, 1mA shock). A speaker was attached to one of the sidewalls to deliver the CS (10 seconds, 2000 Hz, 80 dB auditory tone). Visual, olfactory, and tactile stimuli were arranged within the chambers to create two distinct

contexts. Context A consisted of 3.0% acetic acid, cage lights off, white room lights on, fluorescent red room lights off, fans on, cupboard doors closed, black transport boxes without bedding, and computer monitor off in Room 1. Context B consisted of 1.0% Ammonium, cage lights on, white room lights on, fluorescent red room lights off, fans off, cupboard doors open, white transport boxes with bedding, black floors, and computer monitor off in Room 2.

To quantify freezing behavior, each cage rested on a load-cell platform. The load-cell platform recorded cage displacements in response to the rat's movements. The load-cell activity values, ranging from -10 to +10 V, were digitized at 5 Hz via Threshold Activity Software (Med Associates). The values were transformed into values ranging from 0 to 100, with higher values indicating greater cage displacement. A bout of freezing was defined as a cage displacement under a value of 10 for a period of at least 2 seconds (Maren 1998). The total number of freezing bouts were divided by the total number of bouts possible within the observation period to yield the percentage of freezing for each animal during each trial. The percentage of freezing was the dependent measure used for analysis.

## **Procedure**

The sixty-four Long Evans derived rats were split into two cohorts of thirty-two each and the experiments were conducted at separate times under the same procedures. Within each cohort there were four groups; a forwards conditioned group that received extinction training (FW-Ext), a forwards conditioned group that does not receive extinction training (FW-NoExt), a backwards conditioned group that received extinction training (BW-Ext), and a backwards conditioned group that did not receive extinction training (BW-NoExt). On day one, all sixty-four rats were placed in the conditioning context (Context A) and following a 5-minute baseline period, were subjected to 12 CS (10s, 2kHz, 80dB)/US (2s, 1mA) pairings separated each by 60-second intervals. For

forward conditioned rats (FW-Ext, FW-NoExt) the stimuli were arranged such that the CS always preceded and co-terminated with the delivery of the US. In contrast, animals receiving backward conditioning (BW-Ext, BW-NoExt), were presented with the US which always preceded and coterminated with CS delivery. All animals remained in chambers for 1 min following the last conditioning trial before being returned to their home cages.

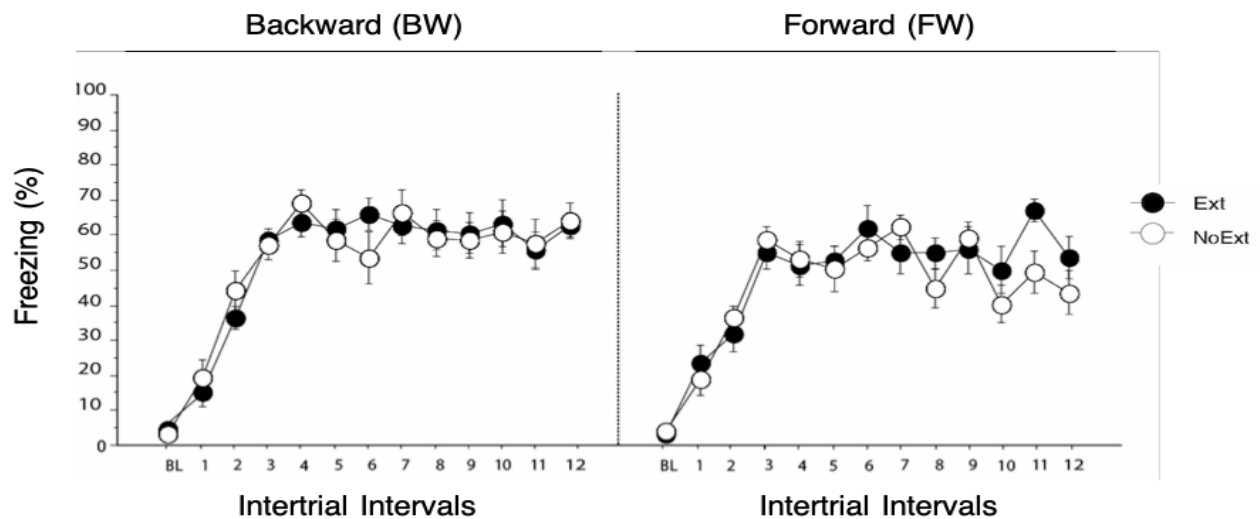
On days 2 and 3, the rats assigned to undergo extinction (BW-Ext and FW-Ext), following a 5-minute baseline period, were subjected to 45 CS (10s, 2kHz, 80dB) presentations separated each by 30-second inter trail intervals in a novel context (Context B). Rats that were assigned to the no extinction groups (FW-NoExt and BW-NoExt) were exposed to a novel context (Context B) without the presentation of the CS or US for the same duration. Following each session, all animals were removed from chambers and immediately returned to their home cages. Context A was used as the main conditioning context; Context B served as the extinction context

On day 4, all rats underwent retrieval testing to the conditioning context (Context A). All rats were exposed to the conditioning context without the presentation of the CS or US for 20 minutes and then were removed from chambers and returned to their home cages after the session.

## CHAPTER III

### RESULTS

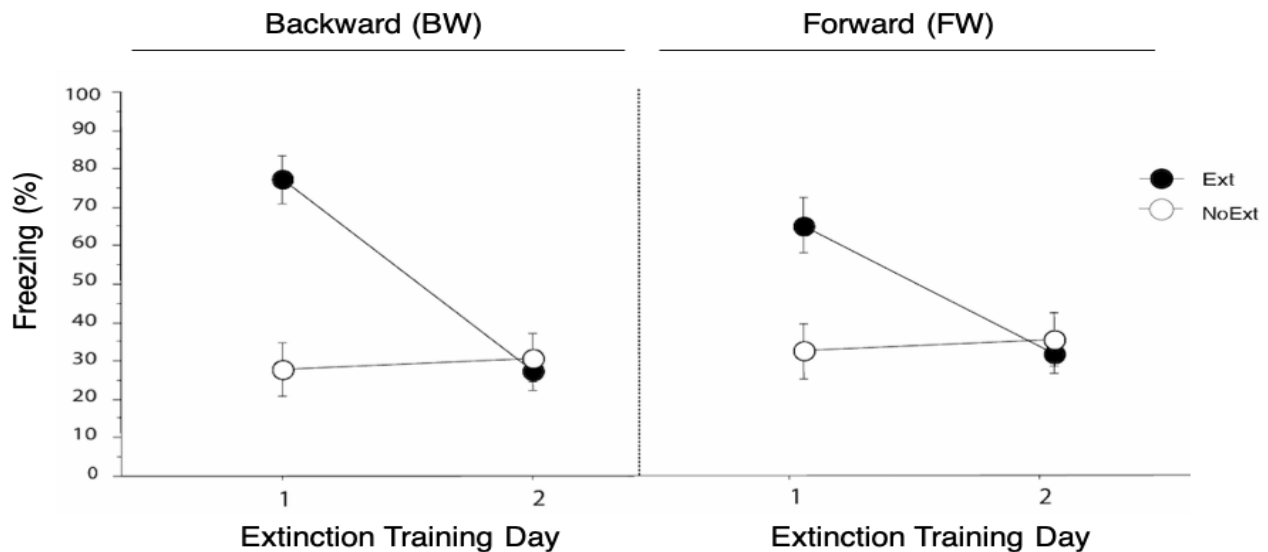
The results from day 1, where the rats underwent either forward or backward conditioning, are depicted in Figure 1. Backwards conditioned rats (BW-Ext, BW-NoExt) exhibited robust freezing during conditioning, indicated by a significant main effect of trial [ $F_{(12,360)} = 44.369, p < 0.0001$ ]. Additionally, there were no differences in trial by group interactions across conditioning [ $F_{(12,360)} = 0.776, p = 0.686$ ]. Forwards conditioned rats (FW-Ext, FW-NoExt) also exhibited robust freezing during conditioning, indicated by a significant main effect of trial [ $F_{(12,360)} = 28.764, p < 0.0001$ ]. Importantly, there were no differences in trial by group interactions across forward conditioned rats [ $F_{(12,360)} = 1.391, p = 0.168$ ].



**Figure 1: Conditioning from day 1 of experiment:** Comparison of percentage of freezing during intertrial interval (60 second post-CS) between extinction (Ext) and no extinction for both forward (FW) and backward (BW) conditioned rats. Baseline (BL) levels of freezing were measured for the first 5 minutes without the presentation of the CS. After which, 12 CS-US (FW) or US-CS (BW) trials were presented, and levels of freezing measured.

The results from days two and three (tone extinction training) are depicted in Figure 2. The results are reported as the first three extinction trials of day two and the last three extinction trials of day three. Backwards conditioned rats revealed significantly attenuated freezing over trials

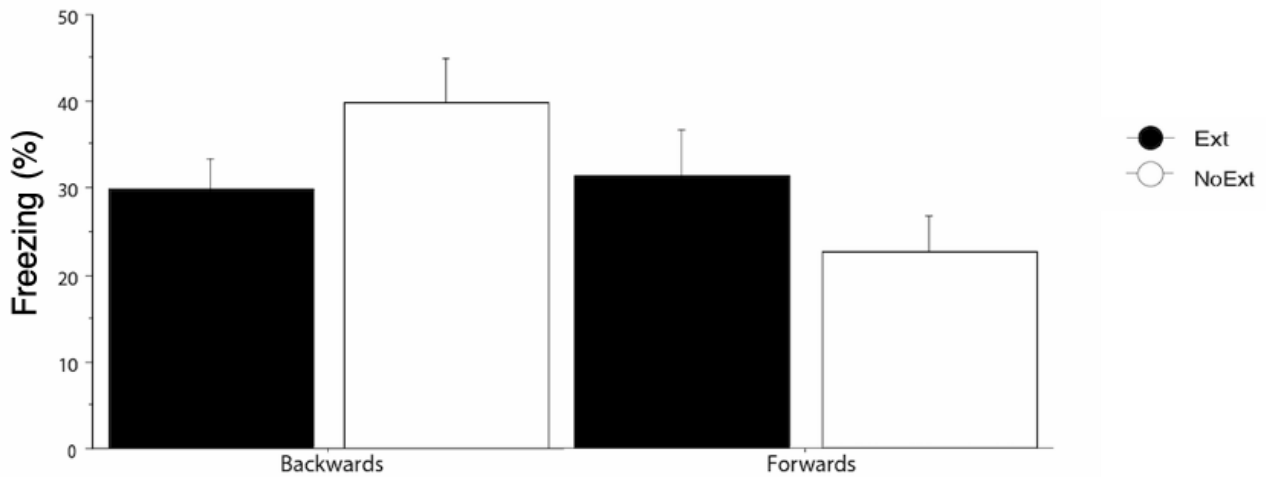
indicated by a significant main effect of extinction [ $F_{(1,30)} = 5.582, p < 0.05$ ]. Additionally, there were no group differences in the last three trials of the second day of extinction training for backward conditioned rats, as revealed by a separate ANOVA [ $F_{(1,30)} = 0.175, p = 0.675$ ]. Forwards conditioned rats also revealed significantly attenuated freezing over trials indicated by a significant main effect of extinction [ $F_{(1,30)} = 15.098, p < 0.001$ ]. There were no group differences in the last three trials of the second day of extinction training for forward conditioned rats [ $F_{(1,30)} = 0.183, p = 0.672$ ]. Importantly, this indicates that forwards (FW) groups with or without extinction training showed similar levels of freezing during the last three trials on the second day of extinction and backwards (BW) groups with or without extinction training showed similar levels of freezing during the last three trials on the second day of extinction.



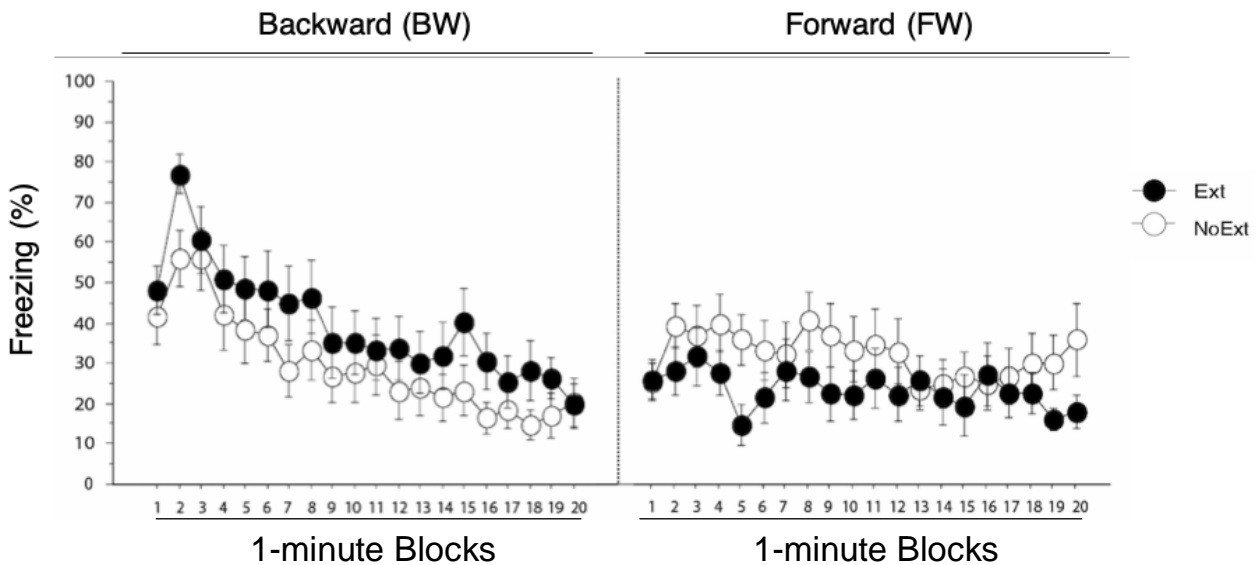
**Figure 2: Context extinction training** for two days (days 2 and 3 of the experiment): Comparison of average percentage of freezing during each day (30-minute sessions per day) between extinction (Ext) and no extinction (NoExt) for both forward (FW) and backward (BW) conditioned rats. Groups that received tone extinction training (Ext) were exposed to the backward (BW) or forward (FW) conditioned tone in a novel context. Groups that did not receive tone extinction training (NoExt) were exposed to a novel context without the presentation of the CS or US.

The results from day four, where we tested the effect of tone extinction training on context-evoked responses, are depicted as an average percentage of freezing in Figure 3. These results indicate that there was a significant group by trial interaction [ $F_{(1,60)} = 4.0, p = 0.05$ ]. The results

from the context test are presented in minute block increments in Figure 4. Backwards conditioned rats revealed nonsignificant but trending main effects of extinction [ $F_{(1,30)} = 2.487, p = 0.125$ ] Forwards conditioned rats also revealed a nonsignificant effects of extinction [ $F_{(1,30)} = 1.604, p = 0.215$ ].



**Figure 3. Average retrieval/CS test from day 4 of experiment:** Comparison of average percentage of freezing during intertrial interval between extinction (Ext) and no extinction (NoExt) for both forward (FW) and backward (BW) conditioned rats. All four groups (FW-Ext, FW-NoExt, BW-Ext, BW-NoExt) received 20 minutes of conditioned context presentation, without the presentation of the CS or the US, and freezing levels were recorded.



**Figure 4. Retrieval/CS test from day 4 of experiment:** Comparison of percentage of freezing during intertrial interval between extinction (Ext) and no extinction (NoExt) for both forward (FW) and backward (BW) conditioned rats. All four groups (FW-Ext, FW-NoExt, BW-Ext, BW-NoExt) received 20 minutes of conditioned context presentation, without the presentation of the CS or the US, and freezing levels were recorded.



## **CHAPTER IV**

### **CONCLUSION**

The goal of this study was to further understand how an animal uses associations between environmental cues and aversive events to resolve temporally ambiguous threat cues. To accomplish this, the present study used CS (tone) extinction in backwards and forwards conditioned animals and fear to the original conditioning context was examined. On the first day of the experiment, animals were first conditioned to either a forward (CS-US) or a backward (US-CS) stimulus. Animals in both forwards and backwards trained groups exhibited robust freezing to the CS alone presentation after day one of the experiment. In forwards groups, the animals acquired predictive value of the CS through a direct association with the US (Rescorla & Wagner 1972). High levels of freezing reported in backwards conditioned rats indicated the use of an indirect CS-US association to acquire a fear response to the CS (Chang et al. 2003). On the following two days, one group of rats of backwards and forwards trained groups underwent tone extinction where they received 45 CS presentations in the absence of the US in a novel context. In other words, the rats acquired new meaning to the CS because it was presented without the US, and as a result, the CS presentation did not hold any associative value. Both backwards and forwards trained rats in this group experienced a reduction in freezing to the CS as a result of extinction training. In addition, a separate group of forward and backward conditioned rats were exposed to the same context as the extinction groups for a corresponding amount of time however did not receive any CS presentations. In this scenario, there was no additional information provided about the CS that could've been used to influence its meaning, so both forwards and backwards trained animals that did not receive extinction training maintained a sustained fear to the CS during

these trials. On the last day, animals underwent retrieval sessions where rats were returned to the conditioning context for a twenty minute increments of time with no presentation of the CS or the US. Levels of freezing were recorded for all sessions and compared for analysis. Of the four groups (FW-Ext, FW-NoExt, BW-Ext, BW-NoExt), animals in the backwards conditioned group that received tone extinction training revealed attenuated freezing response to the conditioning context during retrieval sessions.

The results of the forwards conditioned animals revealed that extinguishing fear response to a conditioned CS was not sufficient in subsequently attenuating fear response to the conditioning context. That is, forward conditioned rats that received tone extinction training did not have a significant attenuation of context fear during retrieval sessions. These data suggest the ability for an animal to use a forwards conditioned CS to elicit a freezing response in preparation for an aversive event is dependent on the predictive value acquired by the CS from the CS-US association. In order for the CS to acquire predictive value from the CS-US association, both the results of the present experiment and other studies suggest that learning about associations between aversive stimuli and novel stimuli in a forwards conditioning trial involves two independent associations (CS-US & US-context) (Rescorla & Wagner 1972). Thus, the degradation of the CS elicited CR acquired from the CS-US association did not influence the additional, independently formed contextually elicited CR acquired from the association between the US and the physical conditioning context. Additionally, a previous study from our laboratory also indicated that reducing a contextually elicited CR via extinction training does not consequentially attenuate freezing responses to a conditioned tone (unpublished observations). That is, the associative value of the physical context is not a consequence of the associative value assigned to the CS in forward conditioning.

The results of the backwards conditioned rats indicated that extinguishing fear to a conditioned CS was sufficient in consequently attenuating fear responses to a conditioned physical context. In fact, these results revealed significantly less freezing in backwards conditioned animals that received extinction training than those in the forwards group that received extinction training (FW-Ext) and in those that were backward trained but did not receive extinction training (BW-NoExt). If the cognitive mechanisms used to resolve a temporally ambiguous cue were identical to those used to resolve a temporally predictable threat cue, then it is likely that degrading the relationship between the CS and the aversive US would not result in subsequent attenuation of fear to the physical context regardless of when the CS was presented in relation to the aversive US. However, in backwards conditioning, there was a significant reduction in fear response elicited by physical context presentation. Thus, these data suggest that a backwards trained CS is fundamentally different than a forward trained CS in that it does not establish a direct associative relationship with an aversive US. That is, the relationship between the CS and the aversive US is indirectly established by means of the physical context (Chang et al. 2003). In other words, in contrast to forward conditioning, the associative value of the physical context is a consequence of the associative value assigned to the CS in backward conditioning.

The results of the present experiment suggest that the cognitive mechanisms that support resolving aversive threat cues may be dependent on whether the cue is temporally predictable or unpredictable (unpublished observations). That is, there are fundamental differences in the cognitive mechanisms used to establish forward conditioned associations and backwards conditioned associations that may suggest that these mechanisms are derived from different neural pathways in the brain. The implications of this research indicate that the effectiveness of behavioral intervention on fear based psychological disorders such as PTSD may be limited by the ability of

the intervention to target the appropriate cognitive mechanisms. For example, by means of temporally predictable threat cues (i.e. FW conditioning), fear based treatment techniques (i.e. exposure therapy) have been moderately successful, but have a high rate of relapse post treatment (Vervliet et al. 2013; Craske et al 2017). These data suggest that the limitations of these types of psychological interventions may be due to the inability of the intervention to impact the indirect associations related to temporally ambiguous threat cues in addition to the temporally predictable cues that are already the focus of such treatments. Thus, implications of this research are beneficial in the effort of developing improved psychopharmacological treatment options for fear based psychological disorders (i.e. PTSD) through further understanding of the cognitive mechanisms that underlie associative learning about a temporally unpredictable noxious event.

The results of the present experiment are limited to behavioral observation. In other words, at no point during the course of the experiment were the animal brains directly interacted with. Rather, indirect influence of cognitive activity was elicited via conditioning and extinction procedures. However, results of this study suggest that there may be fundamental differences in neural pathways associated with this learning about temporally ambiguous and temporally predictable threat cues. Future studies in animal models may utilize pharmacological interventions in an effort to excite or inhibit brain regions that support cognitive mechanism mediating the acquisition of different types of associations. Furthermore, an interesting occurrence was observed where forward conditioned animals who received tone extinction training inevitably exhibited higher rates of freezing than those trained in a forward fashion that did not receive extinction training. An interesting prospective avenue for future research may be a towards focusing on determining the cognitive mechanisms that support the ability for the animal to proliferate freezing

response to other environmental cues when the forwards conditioned CS-US relationship is degraded by extinction training.

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