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Fear Conditioning and Reconsolidation-Blockade in the Treatment of Post-Traumatic Stress Disorder in Emergency Responders

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by

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Abstract

Emergency Medical Technicians (EMTs) are faced with the problem of being repeatedly exposed to potentially traumatic events (PTEs) due to the nature of their profession. This greatly increases their susceptibility to developing Post-Traumatic Stress Disorder (PTSD). This senior project proposes two studies that will help create a profile of PTSD in individuals who are repeatedly exposed to trauma. Both studies employ the use of fear-conditioning paradigms, specifically the measure of spontaneous recovery (SR), to assess severity of PTSD symptoms. The first proposed experiment aims to determine the susceptibility of newly trained EMTs to developing PTSD using a discrimination fear-conditioning task while also taking into consideration factors that influence susceptibility. I hypothesize that the relationship between childhood trauma and spontaneous recovery will be optimal at predicting the severity of PTSD symptoms. The second proposed experiment aims to determine the efficacy of a cognitive process called reconsolidation-blockade in the treatment of EMTs diagnosed with PTSD, specifically against EMT-relevant stimuli. I hypothesize that reconsolidation-blockade will be effective in ameliorating learned fear responses to both EMS-relevant and non EMS-relevant stimuli, but that it will not override the inherent arousal experienced by EMTs upon viewing scenarios depicting people in medical distress. This can be attributed to their training and the alertness with which they are expected to respond to such scenarios. These proposed experiments could further the understanding of the effects of repeated exposure to trauma and provide a foundational basis for examining PTSD through the lens of fear conditioning in emergency responders.

Introduction

The classical fear-conditioning paradigm

The acquisition, retrieval and extinction of fear are explained in a well-established model known as the fear-conditioning paradigm. Conditioned fear is acquired when an aversive stimulus (i.e., one that causes emotional or physical pain) is paired and presented with a neutral stimulus that when presented by itself, does not typically elicit a fear response (Cacioppo & Freberg, 2013). Over time, the pairing of the aversive stimulus with the neutral stimulus creates an association between the stimuli leading to the acquisition of a conditioned fear response. After the association has been cemented in the long-term memory (LTM), the presence of the neutral stimulus alone is enough to cause a fear response (Cacioppo et al., 2013).

This process of associative learning also known as classical or Pavlovian conditioning was first developed by Ivan Pavlov, a Russian physiologist who belonged to the school of behaviorism, which held as its tenant that all behaviors were observable and measurable, making behaviors the most reliable way to study the characteristics of an individual (Cacioppo et al., 2013). In an appetitive association study, Pavlov established an association between two unrelated stimuli in dogs by ringing a bell—the unconditioned stimulus (US)— to signify the arrival of food (conditioned stimulus or CS), which by itself would cause an increase in salivary production—the unconditioned response (UR). For classical conditioning to take place the pairing was repeated many times so the dog would learn the association between food and the aural stimulus. When the dog had learned the association between food and the ringing of the bell, the sound alone would elicit an increased salivary production—the UR (Cacioppo et al., 2013).

Though Pavlov's original experimental design used an appetitive stimulus as a reinforcer, this paradigm can be applied to the acquisition of conditioned fear as well. If a person who fears snakes is hiking through the woods and gets attacked by a snake (unconditioned stimulus or 'US') in a patch of leaves, which causes a rustling sound (conditioned stimulus or 'CS'), their fear response might manifest in paralyzing or freezing behavior (unconditioned response or 'UR'). Because of the association between the snake attack and the sound of leaves rustling, all subsequent times the person hears leaves rustle, they might anticipate the attack/presence of a snake.

Pavlovian reinforcement utilizes repeated pairings with appetitive or aversive outcome associations between various stimuli to control and predict behaviors, but behaviors can also be reinforced by their consequences or outcomes, regardless of the stimulus present or the associations between stimuli (Cacioppo et al., 2013). This is explained through a paradigm known as operant or instrumental conditioning. In instrumental conditioning, an individual learns responses to stimuli based on the outcomes that those stimuli have been associated with in the past. This has an important implication for the development of fear. If the person afraid of snakes is somehow able to overcome their fear and retreat from the snake attack, the action of retreating is a negative reinforcer, allowing the individual to avoid the aversive outcomes (i.e., being attacked by a snake).

There are many steps involved in the acquisition of conditioned fear, each of which involves different neural pathways and cellular mechanisms in different but connected regions of the brain (Johnson, McGuire, Lazarus & Palmer, 2011). The presence or absence of psychological and physiological conditioned responses to fear have been assessed in the psychological literature by a standard fear conditioning paradigm. Within the classical fear-

conditioning paradigm, some important steps that lead to the presence of a conditioned fear response are acquisition, consolidation, extinction, and spontaneous recovery. The timeline of these steps are depicted in Figure 1.

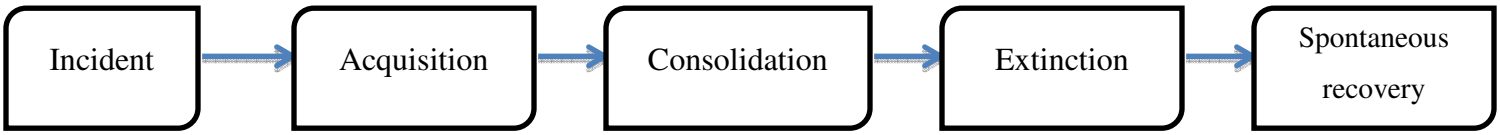


Figure 1: Temporal timeline of events that occur during the classic fear-conditioning paradigm

Fear Conditioning Paradigm: Acquisition

When individuals experience and learn something new, a series of cellular changes occur in their brains that allow the new information to be stored in their LTM. Before the information can be transferred to the LTM, it undergoes a series of modifications from its initial encoding in the short-term memory to its subsequent encoding in the LTM. This process is facilitated by a phenomenon called long-term potentiation (LTP).

LTP is hypothesized to explain the cellular and molecular underpinnings of how memories are formed. Nader & Hardt (2009) state that LTP is a "long-lasting enhancement in signal transmission between two neurons after repeated stimulation" (p. 224). When the brain receives new information, neurons in regions associated with learning such as the amygdala and the prefrontal cortex begin to fire signals (Nader et al., 2009). The signal passes down from the pre-synaptic neuron to the post-synaptic neuron. During this signal transduction, certain ions that flow between neurons are responsible for opening specific receptors on the post-synaptic cell, which are controlled through an ion-gated mechanism (Nader et al., 2009).

The two most common receptors found on the post-synaptic cell are the α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor and the N-methyl d-aspartate

(NMDA) receptor. AMPA receptors allow only positively charged sodium ions to enter the post-synaptic cell, whereas the NMDA receptors permits both sodium and calcium ions. However, the NMDA channel is typically blocked by a magnesium ion, which is only displaced when the signal of the pre-synaptic neuron reaches a certain threshold.

Hence, when neuronal activity of the pre-synaptic neuron is sustained over time, the AMPA receptor allows for a greater state of depolarization in the post-synaptic neuron and the Mg2+ ion unblocks the NMDA receptor to allow more sodium and calcium to flow through it. The sustained activity of the AMPA receptors is what causes the depolarization of the post-synaptic neuron, which ultimately allows for LTP to occur. The NMDA receptor, which only opens when the cell is in the optimum state of depolarization, is also called the coincidence detector, as it is able to detect spatially nearby signals. Since LTP is contingent on this mechanism, it is only when this process occurs that information can be transmitted from the short-term memory to the LTM. Once in the LTM, the memories undergo a process called consolidation, which assists in cementing the memories in the long-term storage.

Fear-Conditioning Paradigm: Consolidation

Nader et al. define consolidation as "a time-dependent stabilization process that leads eventually to the permanent storage of newly acquired memory" (p.224). Once LTP has occurred, the new information gets transferred over to the LTM and undergoes a period of lability, where it is subject to change through external or internal influences. Once this time period has passed, the memory is consolidated (Nader et al., 2009). Although these consolidated memories were once thought to be permanent and impervious to any sort of modification ((Nader et al., 2009; Alberini, 2005), the reconsolidation hypothesis, which will be explained shortly, disproves this notion (Nader et al., 2009; Alberini, 2005).

LTP strengthens the connection between neurons in a group by facilitating synchronous firing. This sustained activity in turn strengthens the memory of the neural pathway being activated, which leads to improved memory function. Long-term potentiation takes place in two phases—the early-LTP phase and the late-LTP phase. While early-LTP does not require gene transcription or protein synthesis to sustain itself, its maintenance into the late-LTP phase is facilitated by protein synthesis, making it a protein-synthesis dependent process. Consolidation, in turn, occurs as a response to protein synthesis (Abel et al., 2001).

Although it is known that the late phase of long-term potentiation (L-LTP) requires protein synthesis for its maintenance, it is unclear how the two are related. Clopath, Zeigler, Vasilaki, Büsing & Gerstner (2008) claim that while the early phase of LTP (E-LTP) is sustained by synchronous firing of a group of neurons, altered, unknown biochemical processes are required for the transition to the L-LTP phase to occur. Additionally, in order for E-LTP to become L-LTP, the presence of newly synthesized plasticity-related proteins is required as they are captured by the tagged synapse (Clopath et al., 2008). Because consolidation is dependent on

a process as basic as LTP, it has been the focal point of memory formation for understanding the mechanisms of learning and retrieval of information (Clopath et al., 2009).

Evolutionarily, the process of consolidation may serve to help information become better integrated with the LTM, since the period of lability can impair or enhance how the new information is perceived (Abel & Lattel, 2001). Abel et al. (2001) identify the hippocampus as the seat of consolidation with evidence from Riedel, Micheau, Lam, Martin, Bridge, Hoz, Poeschel, McCulloch & Morris (1999), who interrupted synaptic transmission in Hooded Lister rats by injecting them with an antagonist of AMPA/kainite glutamate receptors (LY326325). Riedel et al.'s (1999) aim was to measure the use of the hippocampal formation in spatial, declarative and rational memory by blocking the abundantly present glutamate receptors of the hippocampus, which is known to be involved in these memory processes (Riedel et al., 1999). The authors used the technique of reversible local brain inactivation, which is advantageous because it can disrupt or temporarily disable neural activity for specific memory processes without interrupting other processes used at a later time. Through this, Riedel et al. (1999) were able to isolate any hippocampal contribution to the process of memory consolidation.

In order to test the effects of LY326325, Ridel et al.'s (1999) experimental rats underwent a period of training using an open-field water maze without being subjected to any pharmacological interventions. Rats were then divided into groups based on initial performance and given varying time-dependent injections of LY326325 into the dorsal hippocampus over the span of seven days. Control rats showed no decline in task retention, and rats that were given acute, short-lived infusions of LY performed better than controls on the retention test administered sixteen days after training. Animals treated chronically with LY at any time during the seven-day period after training showed impaired memory recall, implying that the

hippocampus plays a vital role in the consolidation of memories, and that the optimal time period for long-term consolidation lasts for at least five days after acquisition (Riedel et al., 1999).

Fear Conditioning Paradigm: Extinction

Myers & Davis (2007) define fear extinction as a "procedure in which a previously fear conditioned organism is exposed to a fear-eliciting cue in the absence of any aversive event…results in a decline in conditioned fear responses" (p. 121). Therefore, for extinction to occur, it is imperative that the paradigm from the aforementioned Pavlovian conditioning is followed. A fear response may be extinguished only if the conditioned stimulus (CS) is presented repeatedly without the unconditioned stimulus (US). This reduces the predictive value of the CS, thereby eliciting a response from the US only and rendering the association between the CS and the US ineffective.

Theories of fear extinction depend on the ways in which CS-US associations are formed, how they can be modified based on the stimulus, and the consequences of the choices. Generally, associations between the CS and US are excitatory (Myers et al. 2007). This association is broken down not because of unlearning, but due to processes within extinction that encompass new learning. The theory of new learning as stated in Myers et al. (2007) postulates that upon presenting the US, the original, conditioned excitatory association is indeed still present, followed by a newly learned, dampening inhibitory association. However, Myers et al. (2007) conclude that extinction most likely emerges from a number of mechanisms working in tandem, which might involve both associative and non-associative methods of learning and unlearning.

Fear extinction takes place in the primary fear structures of the brain- the amygdala, the hippocampus and the medial prefrontal cortex (Bremner, 2006). The amygdala is involved in the

acquisition and expression of fear (Cacioppo et al., 2013). Lesions to the lateral or central nuclei of the amygdala inhibit extinction as conditioned fear is expressed in these regions (Zimmerman, Rabinak, McLachlan & Maren, 2007). However, when lesions are made prior to learning in the basal amygdala, extinction can be studied as this has little impact on the acquisition of fear. This suggests that the nuclei of the basal amygdala are employed for conditioned fear but can be replaced with other regions during extinction due to the substitution by the lateral and central nuclei (Myers et al., 2007).

During the process of extinction training, multiple studies have reported that the amygdala displays temporary activity during the beginning of the session (Gottfried, & Dolan, 2004; Knight, Smith, Cheng, Stein & Helmstetter, 2004; LaBar, Gatenby, Gore, LeDoux & Phelps, 1998) persistent activity during the session (Gottfried et al., 2004) and decreased activation when presented with the reinforcing CS (Phelps, Delgado, Nearing & LeDoux, 2004). This suggests that the amygdala, while crucial to both fear acquisition and expression, plays a role in the extinction of fear as well (Bremner, 2006).

Fear-Conditioning Paradigm: Spontaneous Recovery

Myers et al. (2007) described spontaneous recovery as "a reappearance of extinguished conditioned responses with the passage of time following extinction training in the absence of any further explicit training…the degree of CR recovery is directly related to the length of the retention interval, such that more robust CRs are observed at longer delays" (pp.122). Similar to extinction, spontaneous recovery also requires the presence of Pavlovian conditioning to take place since the conditioned response, which disappears after successful extinction training, is recovered after a passage of time.

Sissons & Miller (2009) claim that for spontaneous recovery to occur, a re-emergence of the initial association to a CS that subsequently has received extinction training must be present. This implies that spontaneous recovery can only take place only once extinction training has been effectively carried out. Rescorla (2004) supports this claim and adds that the measure of spontaneous recovery is likely to be greater as more time passes between the extinction training and the subsequent testing.

Spontaneous recovery supports the idea that learning is a malleable, time-dependent process. Spontaneous recovery indicates the return of a behavior that was purposefully dampened during extinction training. This means that the new information learnt during extinction training (new, inhibitory association) is overpowered by the initial, aversive reaction that was consolidated as a memory when fear acquisition took place (Rescorla, 2004). Because spontaneous recovery is integral to determining the success or failure of extinction, studying the process helps in understanding the mechanisms behind the inhibition of new learning, and how to optimize extinction-training sessions in a therapeutic setting.

Rescorla (2004) argues that the inhibition of the initial fear memory trace dissipates over time, which is what leads to spontaneous recovery. While there is not enough empirical evidence to suggest the presence of any one mechanism being responsible for the occurrence of spontaneous recovery, Bouton (2004) states that spontaneous recovery occurs contingent on temporal and contextual differences. For instance, when an original fear memory trace results in a fear response during a spontaneous recovery test despite extinction training, it can be attributed to a failure to retrieve a memory that was established during the context of extinction. However, Rescorla (2004) maintains that spontaneous recovery is most likely governed by a number of neural processes that are still being explored and understood in the context of the traditional fear-conditioning paradigm.

Fear-Conditioning Paradigm: Reconsolidation

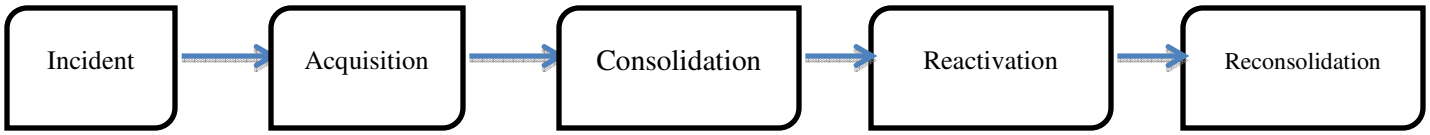


Figure 2. Fear-conditioning paradigm depicting timeline for reconsolidation to occur

After the consolidation of information in the LTM, memories were believed to be permanent and indelible. However, the process of reconsolidation disproves this notion (Nader et al., 2009; Alberini, 2005). The reactivation of an already consolidated memory is followed by a period of lability wherein the memory can be modified (Figure 2), through behavioral or pharmacological means (Schiller et al., 2009). Nader et al. (2009) described reconsolidation as the process where "consolidated memories…can re-enter states of transient instability following reactivation, from which they must again stabilize in order to persist, contradicting the previously dominant view that memory and its associated plasticity mechanisms progressively and irreversibly decline with time" (p.224).

An experiment conducted by Nader, Schafe & LeDoux (2000) evidences the occurrence of reconsolidation in the lateral basal amygdala (LBA), which is considered to be the site of storage for fear memories (Fanselow & LeDoux, 1999). Consolidation of memories requires protein synthesis (Abel et al., 2011). Nader et al. (2000) claim that reconsolidation is also a protein-synthesis dependent process, as protein synthesis is required in the LBA after reactivation of consolidated memories. In the study conducted by Nader, Schafe & LeDoux (2000), adult rats were subjected to pairings of a tone (CS) and a foot shock (US), and their freezing behavior was recorded as the fear response. Twenty-four hours after fear acquisition, rats were either presented with the CS (to reactivate the memory) or not presented with the CS,

and then immediately administered bilateral infusions of anisomycin into the LBA, or artificial cerebrospinal fluid (ACSF) as a control. Some rats received the infusions six hours after reactivation. Anisomycin is a known protein synthesis inhibitor and hence interferes with the process of reconsolidation. Twenty-four hours after the infusion, rats were presented with three CSs and their freezing behavior was recorded.

Results revealed that freezing behavior decreased on a dose-dependent basis, with significantly different results between the rats administered with a low dose of anisomycin (6.2 μg per 0.5 μl per side) or ACSF and those given a high dose of anisomycin (62.5 μg per 0.5 μl per side). This implies that the volume of anisomycin administered must cross a certain threshold in order to successfully inhibit protein synthesis. The fear response for rats that were administered anisomycin without having the memory of the CS reactivated did not alter from the learning phase (Nader, Schafe & LeDoux, 2000), indicating that reactivation is necessary for reconsolidation. These findings also imply that successful reconsolidation and consolidation of memories requires protein synthesis to occur at the optimal window of timing. It also provides evidence that protein-synthesis inhibitors like anisomycin or propranolol have the ability to block reconsolidation, providing a pharmacological means of altering memory traces (Nader, Schafe & LeDoux, 2000). These results provide useful insight into how these pharmacological agents can assist in the therapeutic treatment of disorders related to fear memories, such as Post-Traumatic Stress Disorder.

The timing for the administration of protein synthesis inhibitors is key to understanding the process of reconsolidation. Anisomycin administered 6 hours after the memory reactivation (presentation of the CS) revealed no decrease in the freezing behavior during the test (Nader, Schafe & LeDoux, 2000), implying that unless reconsolidation is blocked during the optimum

period of lability, the memory undergoes the process of reconsolidation and cements itself once more in the LTM. Reconsolidation strengthens consolidated memories after retrieval occurs, but only if the process of reconsolidation is not blocked during the period of lability by pharmacological or behavioral means.

While consolidation and reconsolidation both serve to cement memories and associated information in the LTM, there are differences between the two processes. A review of memory consolidation and reconsolidation by Alberini (2005) revealed that multiple studies that used protein-synthesis inhibitors on animal models immediately after retrieval of consolidated memories noted an impairment in memory retention at a later time (Child, Epstein, Kuzirian & Alkon, 2003; Kida, Josselyn, Pêna de Ortiz, Kogan, Chevere, Masushige & Silva, 2002; Lattal et al., 2004; Pedreira, Pérez-Cuesta, & Maldonaldo, 2002). This indicates that the functional purpose of both consolidation and reconsolidation is to integrate new information into the LTM. However, reconsolidation and consolidation can be thought of as distinct processes as they differ on some cellular and molecular levels. For example, Lee, Everitt & Thomas (2004), who specifically targeted contextual fear memory in the hippocampus of rats, revealed that brain-derived neurotrophic factors (BDNF; a protein related to other growth factors) were involved in the process of consolidation, but were not required for reconsolidation to successfully take place. Inversely, reconsolidation required the presence of a certain transcription factor, Zif268, which consolidation did not require. Hence, while both systems serve to update memory, reconsolidation is not merely a repetition of consolidation, but rather a distinct process that requires different cellular changes to be successful.

Lee et al. (2004) also take into account the circumstances under which consolidation and reconsolidation occur—consolidation requires the presence of the reinforcing, aversive stimulus

while reconsolidation only requires the reactivation of the CS without the aversive stimulus—and admit that these impositions make the comparison difficult. The interruption of consolidation causes the initial encoding of memories in the LTM to be disrupted, whereas the interruption of reconsolidation can either modify the emotional information associated with a memory by strengthening or dampening these relations.

Rodriguez-Ortiz & Bermúdez-Rattoni (2007) argue that reconsolidation works as an update mechanism to the process of memory integration. Evolutionarily, reconsolidation may serve to better integrate updated, new information regarding memories into the LTM through protein synthesis. When this process is disrupted, it partially destabilizes the information that became consolidated as a memory in the LTM (Rodriguez-Ortiz et al., 2007). This process is known as "reconsolidation-blockade" and can be induced in a laboratory setting using beta-blocker protein synthesis inhibitors such as anisomycin or propranolol. Reconsolidation-blockade can also be achieved through behavioral means like extinction training when it is provided after the reactivation of the memory.

Reconsolidation-blockade has beneficial implications for the treatment of PTSD. PTSD is a disorder of fear conditioning wherein the continuous, spontaneous re-experiencing of traumatic memories and the fearful associations made with these memories can cause significant functional impairment in the lives of the affected. Reconsolidation serves to destabilize previously consolidated memories, therefore the blocking of reconsolidation allows for fearful associations to be modified or eradicated completely in the optimum window of time after re-activation. Many studies have shown evidence for a diminished fear response after the administration of reconsolidation-blocking agents or behavioral therapies that integrate new information into the previously consolidated memory (Schiller, Monfils, Raio, Johnson, LeDoux & Phelps, 2009;

Kindt, Soeter & Vervliet, 2009; Soeter & Kindt, 2011; Schiller, Raio & Phelps, 2012; Steinfurth, Kanen, Raio, Clem, Huganir & Phelps, 2014). Since reconsolidation-blockade in the form of pharmacological agents or behavioral extinction training has the potential to eradicate the fear associated with memories while leaving the memory itself intact, it could help to enhance the treatment of PTSD. However, pharmacological testing of propranolol on humans reveals side effects like increase in depression & fatigue (Head, Kendall, Ferner & Eagles, 1996), which make behavioral reconsolidation-blockade a much more appealing option for PTSD treatment.

Behavioral reconsolidation-blockade can be carried out in the form of extinction training during the optimum window of time after reactivation of memories (Nader et al., 2000; Steinfurth et al., 2014; Monfils et al., 2009). Extinction training in the lab and in a therapeutic setting consists of exposing the affected individual to the CS that causes their PTSD, but without the presence of any aversive stimulus, so that the individual may learn that the CS does not have to be associated with fear. Persistent presentation of the CS in the absence of the aversive stimulus eventually leads to a diminished or absent fear response. The new learning that takes place during extinction training serves to update the emotional information about the memory associated with the CS. Reconsolidation-blockade is emerging as a novel and empirically beneficial cognitive process in the treatment of PTSD as it aims to modify the cognitive changes that occur in the individual rather than just the observable behaviors.

Post-Traumatic Stress Disorder

PTSD is categorized as a 'Trauma and Stressor-Related Disorders' as per the latest edition of *The Diagnostic and Statistical Manual of Mental Disorder* (DSM-5) (5th ed.; DSM-5; American Psychiatric Association, 2013). In this disorder, direct or indirect exposure to a traumatic or stressful event is an explicit criterion for diagnosis. The DSM-5 states several criteria that must be met in order for a diagnosis of adult PTSD to be made by a clinician. Criterion A is "Stressor", which denotes the kinds of experiences that constitute a trauma as specified by the DSM. These experiences could be direct exposure (i.e., witnessing in person), indirect exposure by learning of an event that affected a loved one, or repeated, extreme indirect exposure to aversive details of the event, typically in the course of professional duties (American Psychological Association, 2013). Criterion B focuses on the intrusive aspects of the disorder that manifest themselves after the traumatic or stressful event has occurred. These include recurrent, involuntary and intrusive memories, nightmares, dissociative reactions like flashbacks, intense or prolonged distress upon being exposed to traumatic reminders, and marked physiologic reactivity after exposure to trauma-related stimuli. Out of these, at least one symptom must be experienced for the diagnosis to be made (American Psychological Association, 2013). Criterion C concerns the avoidance aspect of the disorder—a persistent effort is made to avoid trauma-related thoughts or feelings, as well as any external reminders of the traumatic event itself (American Psychological Association, 2013).

While Criterion A-C primarily focuses on the observable signs and complaints of the disorder that impact the patient's body, Criterion D focuses on the cognitive impact that PTSD exerts on patients. In PTSD, after a traumatic event, patients usually experience an impairment in their ability to recall key features of the trauma, persistent negative beliefs about the future or the

perception of the self, distorted blaming of self or others as the cause of the event, persistent negative trauma-related emotions, significantly diminished interest in (pre-trauma) significant activities (anhedonia), or constricted, flat affect. A minimum of two symptoms from this category is needed for the diagnosis to be made (American Psychological Association, 2013). Criterion E addresses the physiological changes that PTSD causes. These include irritable or aggressive behavior; self-destructive or reckless behavior; hypervigilance, exaggerated startle responses, problems with concentration and sleep disturbance (American Psychological Association, 2013). Out of these, a minimum of two symptoms must be present for the diagnosis to be made, and all symptoms must be experienced for longer than one month (Criterion F) (American Psychological Association, 2013). Criterion G specifies that symptoms must cause some significant distress or functional impairment and Criterion H covers exclusion (symptoms must not be cause due to medication, pharmacological interventions, or other illnesses) (American Psychological Association, 2013). In order for a clinician to make a diagnosis of PTSD, all criteria mentioned in the DSM-V must be met.

After a diagnosis is made, clinicians create a course of treatment designed to eradicate the signs and symptoms of a patient's PTSD. Typically this treatment falls under the general purview of already well-established therapeutic routes such as cognitive-behavioral therapy (CBT) or exposure therapy (Kar 2011; Rothbaum & Schwartz 2002). Though both CBT and exposure therapy have shown to be effective in treating some symptoms of PTSD (Kar 2011; Rothbaum et al., 2002), these treatments are limited in that they do not modify the original fear memory trace. Thus in order to truly eliminate the symptoms of PTSD, treatment must adhere to individual needs and differences such that the basic emotion of fear in response to trauma-related cues is eliminated. The elimination or modification of fear as evoked by the traumatic fear

memory should help PTSD patients experience and remember their traumatic event(s) without evoking the previously associated negative physiological and psychological reactions. Reconsolidation-blockade is not a treatment option by itself, but is a cognitive process that can be incorporated into existing therapies. Reactivating the fear memories prior to providing extinction training is more efficacious in ameliorating PTSD symptoms than simply providing extinction training alone (Nader, Schafe & LeDoux, 2000; Schiller et al., 2009).

Understanding PTSD through the fear-conditioning paradigm

Because the development and maintenance of PTSD is contingent upon an intact fear memory of the traumatic event, fear conditioning is emerging as a novel and important way to learn more about the treatment, prevention and predisposition towards PTSD. Mahan & Ressler (2012) claim that what establishes the link between PTSD and fear conditioning is the generalized fear response that a patient develops after a traumatic event to situations that would be considered safe and fear-free. Autonomic hypervigilance, re-experiencing (intrusion) and avoidance—three major symptom classes of the disorder—contribute to feelings of anxiety and fear upon encountering any scenarios reminiscent of the trauma or during day-to-day activities (American Psychological Association, 2013). This is analogous to the classical fear-conditioning paradigm in that being subjected to the CS in the absence of the US once a fear association has been formed is enough to invoke a fear response. Additionally, fear conditioning paradigms are robust and easy to interpret because they produce reliable physiological as well as behavioral changes, making this approach a tractable method of studying PTSD.

In addition to providing a conceptual framework for understanding PTSD, responses to fear conditioning may also explain individual differences in the propensity to develop PTSD.

Although PTSD must arise out of direct or indirect exposure to a traumatic event, not everyone that experiences a potentially traumatic event develops PTSD. The influencing factors that predispose an individual to developing PTSD after experiencing a traumatic event are the topic of many current research pursuits. Mahan et al. (2012) argue that individual differences that create vulnerability to PTSD include genetic make-up, early life events, predisposition, temperament and social support network. In addition to these factors, what is common to PTSD patients is the finding that they show a higher amount of sensitivity to stress, over-generalization of fear associations and failure to extinguish learned fear, seating the basis of PTSD in fear learning pathways (Mahan et al., 2012). Thus, many of the individual differences that create vulnerability to the disorder are related to responses measured in canonical fear conditioning experiments.

Given that a number of factors predisposing certain individuals to developing PTSD have been established, understanding the mechanistic basis of these factors is critical for developing effective clinical interventions. Neuroimaging and animal research studies provide evidence for the pathways that cause individuals to develop PTSD. Francati, Vermetten & Brenmer (2007) conducted an overview of neuroimaging studies on animal and human models with post-traumatic stress disorder to conclude that aberrant synaptic plasticity, which is the change that occurs along the synapse when neuronal activity is sustained for a period of time, underlies the mechanism of PTSD. This abnormal plasticity is most profound in the three limbic brain regions associated with PTSD, fear learning and emotion regulation (Bremner, 2006). These three regions—the amygdala, hippocampus and prefrontal cortex—all contain underlying, interlinked neural pathways that work in tandem to execute the processes involved with the classical fear-

conditioning paradigm, and hence serve as important focal regions for the study of PTSD (Francati et al., 2007; Bremner, 2006).

Synaptic plasticity occurs in these regions of the brain when they receive new information (Nader et al., 2009). At the time of the traumatic incident, synaptic plasticity functioning is normalized, and the associations made between aversive stimuli and neutral stimuli are easily learned with the plasticity intact. What changes with the development of PTSD is the functioning of synaptic plasticity (Francati et al., 2007). Hence, any learning that occurs after the traumatic incident occurs in the presence of abnormal synaptic plasticity. When this plasticity is aberrant, it interferes with the formation of new associations between stimuli, thereby preventing patients with PTSD from making new associations to the neutral stimuli that would help negate the fear memory trace.

Zovkic & Sweatt (2012) elucidate why fear conditioning provides an easy, robust model to study and treat PTSD through the use of animal models such as rodent and zebra fish. The first benefit is being able to subject animals to well-controlled, ethically sound traumatic experiences (Zovkic et al., 2012). This is also advantageous for the purpose of memory as the trauma can be experienced until the conditioned response (CR) is elicited by the conditioned stimulus (CS), indicating that the association of fear to the aversive, unconditioned stimulus (US) has been generalized to trauma-related cues (i.e., the CS) (Zovkic et al., 2012). Zovkic et al. (2012) also expound the value of re-exposing the animal to trauma-related cues in these studies in order to model recurrent memories of the traumatic event in PTSD patients. The brain areas associated with fear conditioning are also active in the expression of PTSD symptoms (Zovkic et al., 2012). Therefore, studying fear conditioning can help to differentiate between normalized and pathological behaviors, and identify cellular and genetic mechanisms of the disorder.

Behaviorally, fear conditioning paradigms are easy to interpret and extremely susceptible to minute, observable changes upon the manipulation of the severity of the trauma, strength of the fear memory trace or clinical interventions. This enhances our understanding of the disorder in humans, and also provides a platform for the pharmacological testing of potentially helpful drugs and therapeutic interventions.

The following two chapters outline the methodology, measures, statistical analyses, predicted results and discussions for two proposed experiments. The first experiment aims to assess the susceptibility of newly trained Emergency Medical Technicians (EMTs) to developing symptoms of PTSD in their first six months of duty by using a discrimination fear-conditioning task. This proposed experiment also considers other factors that influence susceptibility to developing PTSD, such as childhood trauma, number of exposures to traumatic calls and concurrent symptoms of trauma/PTSD. The second experiment aims to determine the efficacy of reconsolidation-blockade in the treatment of EMTs diagnosed with PTSD using a discrimination fear-conditioning task. The experiment, which uses EMS-relevant and non EMS-relevant stimuli, also aims to assess the usefulness of reconsolidation-blockade against stimuli that serves as a trigger for the cohort's PTSD, and is also associated with their day-to-day lives through their profession.

Study I: EMT Susceptibility to PTSD Symptoms

Introduction

Studies have shown that 5-15% of individuals that experience a potentially traumatic incident develop PTSD (Cohen, Zohar, Matar, Zeev, Loewenthal & Richter-Levin, 2004; McNally, 2012; Yehuda & Flory, 2007), implying that certain individuals possess resilience against or susceptibility to developing PTSD. Susceptibility to developing strong and persistent reactions to traumatic incidents has been associated with poor social networks and lack of support (Mealer, Jones & Moss, 2012), professional stressors, self-blame (Meyer, Zimering, Daly, Knight, Kamholz & Gulliver, 2012), childhood abuse, and number of exposures to trauma (Wrenn, Wingo, Moore, Pelletier, Gutman & Bradley, 2011). When PTSD was initially being understood and treated, clinical interviews and assessment scales were structured in a way that would allow the patient to link their symptoms to just one traumatic incident. However, it is becoming apparent that PTSD can be caused by multiple factors interacting with one another, especially when multiple instances of trauma are involved (Williams, Williams, Stein, Seedat, Jackson & Moomal, 2007).

This increased interest in the effects of repeated exposure to trauma is reflected in the APA's addition to the causes of stressors (Criterion A) in their DSM-V definition of PTSD. It states, "Repeated or extreme indirect exposure to aversive details of the event(s), usually in the course of professional duties (e.g., first responders, collecting body parts; professionals repeatedly exposed to details of child abuse). This does not include indirect non-professional exposure through electronic media, television, movies, or pictures" (American Psychiatric Association, 2013). This description of potential causes of PTSD reveals the growing need to understand the neurological, physical and behavioral effects of repeated exposure to trauma, and

design clinical interventions that are catered to ameliorate negative symptoms that arise from the same. Individuals will habitually be exposed to potentially traumatic events through first response professions such as the police force, firefighting and emergency medical response.

The nature of emergency response requires resilience towards traumatic incidents, especially because an EMT or paramedic may experience multiple potentially traumatic events (PTEs) during their professional career and even within a single shift (e.g. death, gory physical injury, suicide attempts, etc.). The nature of the job of an EMT may exacerbate an individual's pre-existing susceptibility to developing PTSD/concurrent symptoms of PTSD due to the unavoidable re-experiencing of trauma and having to remain in a state of hypervigilance during shifts (Donnelly & Siebert, 2009; Donnelly, 2012). It is important to consider that EMTs diagnosed with PTSD cannot avoid triggers of their traumatic incident if they chose to continue serving as first-responders, causing more distress. A review of the literature on EMS risk factors revealed that 80-100% of EMTs experienced exposure to traumatic events, and 20% reported presence of post-traumatic symptomatology (Donnelly et al., 2009). Additionally, alcohol and drug usage in EMTs was approximately 40% (Donnelly et al., 2009), which reveals the growing need to focus on appropriate treatment options for this cohort.

The process of spontaneous recovery can help explain the symptoms of intrusion and re-experiencing in PTSD patients. For an affected EMT, spontaneous recovery can be understood as a sudden, unanticipated re-emergence of fear-inducing associations between a neutral stimulus (i.e., responding to a medical emergency) and an aversive outcome (e.g., death, blood, physical injury, psychological emergencies) that were either thought of as harmless or naturally forgotten (extinguished). For example, an EMT who is affected by a traumatic call that involved blood

may become triggered by the sight and smell of blood, and the traumatic memories associated with the call might resurface even when the EMT is not actively working.

In a controlled laboratory setting, spontaneous recovery can be assessed after extinction training is successfully completed. Spontaneous recovery, which constitutes the symptom of re-experiencing of trauma, can be operationalized using skin conductance response (SCR). SCR is measured by placing electrodes on the fingers, which measure changes in electro-dermal activity. For example, when a person experiences fear, a common physiological response is an increased production of sweat, which translates into higher electro-dermal activity as measured by the electrodes (Cacioppo et al., 2013). Hence, it is possible to use skin conductance to study fear conditioning and PTSD, and to apply the trajectory of the traditional fear-conditioning paradigm to understand the development of PTSD.

The proposed experiment aims to assess the spontaneous recovery of newly trained EMTs using a generalized fear-conditioning task, and to use this information to determine if the level of spontaneous recovery can predict future severity of PTSD symptoms. Since it is known that number of traumatic incidents and childhood trauma are susceptibility factors to developing PTSD (Wrenn et al., 2011; Williams et al., 2007), the study will account for these factors to establish whether they influence susceptibility for individuals who experience repeated exposure to trauma. I hypothesize that individuals who have a greater measure of spontaneous recovery as well as a high amount of childhood trauma will be most susceptible to developing PTSD from their work as EMTs. A higher measure of spontaneous recovery will be indicative of greater susceptibility to re-experiencing traumatic memories, which is one symptom of PTSD (intrusion).

Methods

Participants

One hundred volunteers (21-60 years old, 50 female) will be recruited from amongst students taking the Emergency Medical Technician-Critical Care (EMT-CC) course offered in New York City, NY. All volunteers will have successfully completed the EMT-CC practical skills and written examinations and would be ready to begin working with various emergency response teams in New York City. None of the participants should have any prior experience with emergency medical response, and all participants should be neurologically and psychologically healthy, with no history of mental illness. None of the participants should report taking any medications for psychological purposes during the time of the study. All participants will be cognizant of the details of the study in order to obtain informed consent, and the study will be submitted to the Institutional Review Board for human subject research at Bard College to receive approval (See Appendix for consent and debriefing forms).

Procedure

This experiment will use a longitudinal design. Phase I will take place over the course of three days, and Phase II will occur six months after Phase I, and will involve one day of clinical assessment. On Day 1 of Phase I, a fear conditioning discrimination paradigm with partial reinforcement of shocks will be used to induce an acquired fear response to a neutral stimulus. Prior to the task, all participants will undergo a calibration procedure to determine a level of shock that is 'highly irritating but not painful' by rating different intensity levels of shocks on a scale of zero (no sensation) to 10 (highly irritating but not painful) until they evaluate a frequency as 10. These intensities of shocks will be generated using the Coulbourn Transcutaneous Aversive Finger Stimulator (E13-22; designed for human research), which

employs a 9-V dry cell battery attached to an adjustable step-up transformer. The skin conductance response (SCR) as well as electric shock calibration will be recorded using apparatus described in the SCR section. Prior to the experiment and using the established comfortable level of voltage, the baseline skin conductance of all participants will be measured for two minutes, in the absence of any stimulus. Any participant with SCR amplitude of less than 0.05 μSiemens will be excluded from the study as per protocol stated in Wood, Ver Hoef & Knight (2014).

Participants will view two colored squares (A and B) on a computer screen placed 60 cm away from the face for 10s per square, one square at a time. Square A will not be associated with any aversive outcome (Conditioned Stimulus -; CS-), whereas viewing square B will generate a mild electric shock to the non-dominant hand of the participant on 38% of all trials (Conditioned Stimulus +; CS+), as per the protocol stated in Schiller et al (2009). All participants will undergo 20 trials, and participants that do not show an increase in their SCR as compared to baseline will be excluded from the study. Twenty-four hours after Day 1, participants will return to the lab for extinction training (Day 2). On Day 2, participants will be shown the same two coloured squares, A and B. However, in order to extinguish the association between square B and the mild electric shock (unconditioned stimulus; UCS) that was established on Day 1, neither square A nor square B will be associated with shocks on Day 2. Extinction training will end after the SCR of participants reaches their baseline measure upon viewing square B. The number of trials each participant needs to extinguish the association between the UCS and square B will be recorded and accounted for in the final analysis. Twenty-four hours past this, participants will come back into the lab to measure their spontaneous recovery (Day 3). Participants will view square A and square B one time without any shocks (UCS), which will help in calculating the measure of

spontaneous recovery. Spontaneous recovery will be measured as ((SCR from Day 3) – (last trial of extinction on Day 2)) as per protocol stated in Schiller et al. (2009).

Skin Conductance Ratings

SCR will be recorded using the Coulbourn Transcutaneous Aversive Finger Stimulator and Coulbourn Isolated Skin Conductance coupler (V71-23). 9mm (sensor diameter) Invivo Metric Ag/AgCl electrodes will be placed on the distal phalanx of the middle and ring fingers of the non-dominant hand as per protocol dictated in Fowles, Christie, Edelberg, Grings, Lykken, & Venables (1981). Electrodes will be placed 14 mm apart from each other. The Coulbourn Lablinc Analog to Digital converter (V19-16) will digitize the SC analog signal at 1000 Hz. All measurements of SCR will be recorded on a Mac-compatible computer and custom designed software provided by Coulbourn Instruments.

Survey Measures

Davidson Trauma Scale (DTS)

Prior to undergoing the fear-conditioning paradigm, all participants will be asked to complete the Davidson Trauma Scale (DTS; Davidson, Book, Colket, Tupler, Roth, David, Hertzberg, Mellman, Beckham, Smith, Davison, Katz & Feldman, 1997) in order to control for any current, pre-existing symptoms of traumatic stress from previous PTEs. The DTS is a 17-item self-report measure that assesses for the presence, frequency and severity of DSM-4 defined symptoms of PTSD. The DTS is useful in determining the presence and severity of PTSD symptoms regardless of whether a participant has been clinically diagnosed with PTSD. This makes it possible to evaluate whether participants are experiencing some symptoms of PTSD without having the disorder itself. Statistical analysis will take the scores of the DTS into account to assess if current symptoms of PTSD affect susceptibility to developing the disorder. For the

frequency aspect of the questionnaire, Davidson et al. (1997) reported a Cronbach's alpha of 0.97, while severity had a coefficient of 0.98. The test-retest reliability of the DTS was determined as 0.86 (p<0.0001) (Davidson et al., 1997).

Childhood Trauma Questionnaire (CTQ)

Some factors affecting an individual's susceptibility to developing PTSD are the intensity, frequency and severity of trauma experienced during childhood (Burri, Maercker, Krammer & Simmen-Janevska, 2013). Since susceptibility to developing PTSD symptoms is influenced by childhood trauma, participants will be instructed to fill out the Childhood Trauma Questionnaire (Bernstein & Fink, 1998) before the fear-conditioning task to account for any influence that childhood trauma might have on developing PTSD symptoms as an EMT. The Childhood Trauma Questionnaire is a 28-item self-report questionnaire that addresses the levels in five types of maltreatment that one might experience during childhood: emotional abuse, physical neglect, emotional neglect, sexual abuse, and physical abuse. CTQ has a Cronbach's alpha of 0.95 (Bernstein, Stein, Newcomb, Walker, Pogge, Ahluvalia, Stokes, Handelsman, Medrano, Desmond & Zule, 2003), and Fink and Bernstein (1997, 1998) found that psychiatrically referred groups reported higher levels of neglect and abuse than the normative population, making the construct validity of this measure quite robust.

Clinician Administered PTSD Scale for DSM-V (CAPS-V)

The CAPS-V (Blake, Weathers, Nagy, Kaloupek, Gusman, Charney & Keane, 1995; Weathers, Keane & Davidson, 2001) test will be administered to all participants during the longitudinal follow-up. CAPS-V is a 30-item structured clinical interview that is effective in

making a current or lifetime diagnosis of PTSD and can also assess PTSD symptoms experienced in the recent past (Blake et al., 1995). Questions target not only the duration of symptoms described in the DSM-5, but also subjective distress, impact of symptoms on social and occupational functioning, overall response validity, and overall PTSD severity. Inter-rater reliability for global severity correlation is 0.89 (Hovens, Van Der Ploeg, Klaarenbeek, Bramsen, Schreuder & Rivero, 1994). Overall Cronbach's alpha for CAPS-V is 0.94 (Blake et al., 1995).

Longitudinal Follow-Up

Six months after completing the fear-conditioning task, all participants will be asked to return to the laboratory to assess the presence and severity of PTSD symptoms. During these six months, all participants will be working as EMTs with various organizations and precincts within New York City. In order to control for the effect of individual experiences, all participants will be instructed to keep a tally of all emergency response calls deemed 'traumatic' during the six months in between Phase 1 and Phase 2. These will be defined to fit Criterion A of the DSM-V's diagnosis for PTSD ("Stressor: Direct exposure, witnessing, learning about death, threatened death, actual or threatened serious injury or sexual violence; or repeated, extreme exposure to aversive details of the event usually in the course of professional duties") (American Psychological Association, 2013). Although participants will be asked to determine whether calls fit this criterion in order to homogenize the definition of "traumatic call", they will be encouraged to rate calls subjectively (i.e., if a call does not fit the DSM-V criterion, but feels traumatic to the individual, it will still be considered a "traumatic call"). Participants will be asked to abstain from writing down details of any traumatic calls, since studies have shown that writing about trauma can influence the associations with traumatic memories (Gidron, Peri, Connolly & Shalev, 1996; Sloan, Marx & Greenberg, 2011). At the follow-up, participants will

undergo a structured, clinical interview using the CAPS-V (Blake et al., 1995) test. If participants score higher than 45 on the CAPS-V scale, they will be given a diagnosis of PTSD. However, for this study, I will be assessing the severity of PTSD symptoms/post-traumatic symptomatology for all participants regardless of whether a clinical diagnosis is made.

Statistical Analysis

All statistical analyses will be carried out with the Statistical package for the Social Sciences (SPSS) Version 21.0 for Mac (SPSS Inc., Chicago, Illinois). The dependent variable (DV) will be the severity of PTSD symptoms as measured by the overall CAPS-V scores for individual participants. The independent variables will be scores on the CTQ, the tally for number of traumatic calls experienced, spontaneous recovery at the end of Phase I, and the number of trials it took to extinguish the fear association on Day 2 of Phase I (Extinction Trials). The statistical analysis will model the main effects for scores on the CTQ, the tally number of traumatic calls experienced, measure of spontaneous recovery, and the extinction trials. Additionally, the analysis will also include an interaction between the scores on the CTQ and levels of spontaneous recovery that affect PTSD symptom severity. A hierarchical regression analysis will be used. In Step 1 of the analysis, all main effects of interest will be entered as predictor variables, as well as the scores on the DTS (statistical control). In Step 2, the interaction between scores on the CTQ and measure of spontaneous recovery will be included to the predictor variables entered in Step 1. ΔF (change in F statistic) between Step 1 and Step 2 will be used to determine significance. This analysis will help determine whether Step 2 of the equation is better at predicting PTSD symptom severity than Step 1.

Predicted Results

Step 1 of the linear regression will reveal a main effect for all independent variables (see Figures 3-5), wherein a higher measure of spontaneous recovery, and greater number of extinction trials and greater number of traumatic calls will predict higher PTSD symptom severity/higher scores on the CAPS-V. Step 2 will reveal an interaction between CTQ scores and spontaneous recovery from Phase I in predicting the severity of PTSD symptoms (Figure 6).

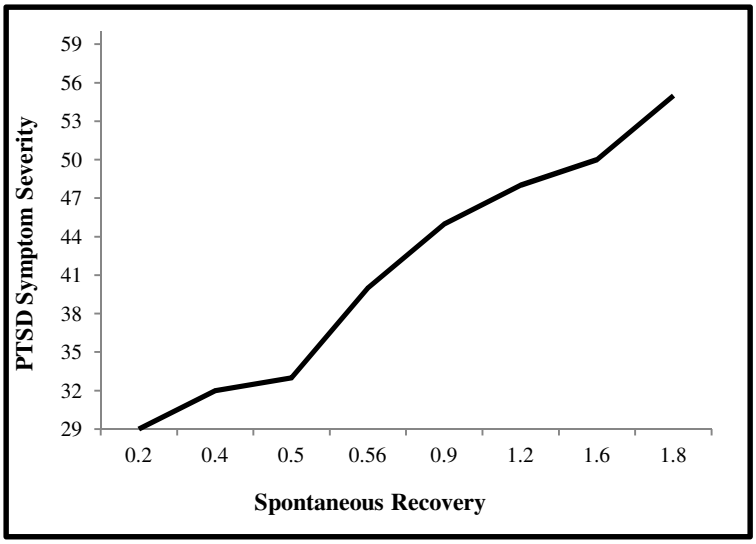


Figure 3. Individuals who will record a higher measure of spontaneous recovery on the fear-conditioning task will also score higher on the CAPS-V, indicating that a high measure of spontaneous recovery is a predictor variable for the development of PTSD symptoms.

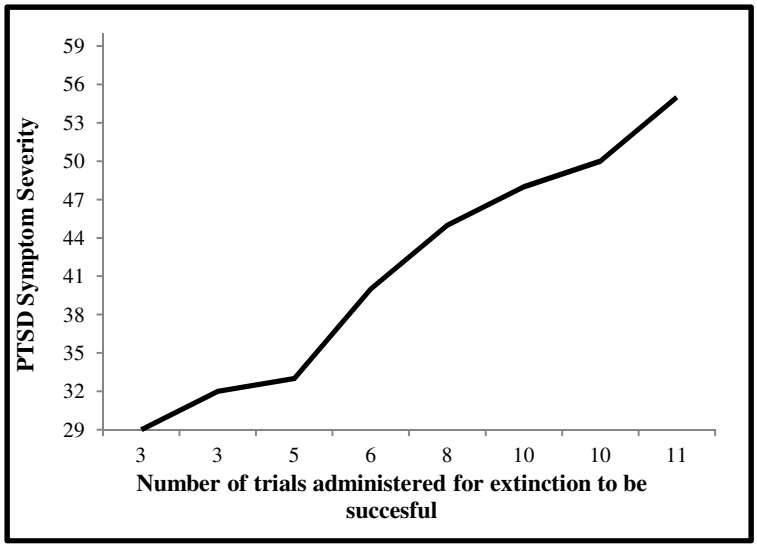


Figure 4. Individuals that need more extinction trials to extinguish the fear association acquired on Day 1 (i.e., number of extinction trials) will also score higher on the CAPS-V, indicating that a greater number of extinction trials is a predictor variable for the development of PTSD symptoms.

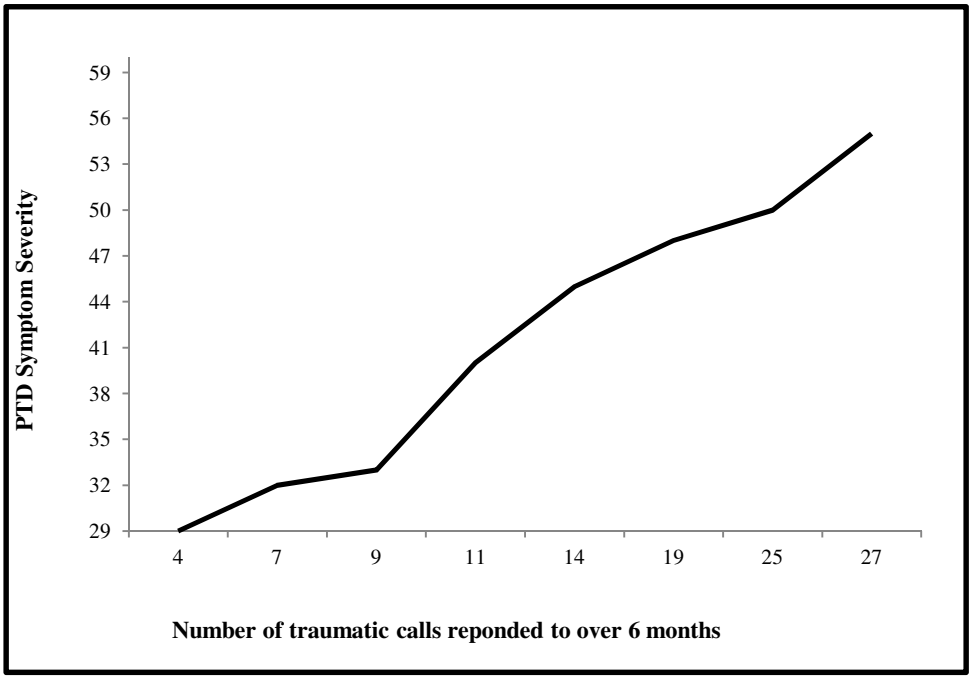


Figure 5. Individuals who will respond to a greater number of traumatic calls during the six-month period will score higher on the CAPS-V, indicating that the number of exposures to potentially traumatic events is a predictor variable for the development of PTSD symptoms.

The ΔF will be significant, indicating that Step 2 will be significantly better at predicting PTSD symptoms severity than Step 1. This result will confirm the importance of the interaction between scores on the CTQ and the measures of spontaneous recovery. Participants with higher scores on the CTQ as well as relatively high measures of spontaneous recovery will have higher scores on the CAPS-V scale, as compared to those participants with lower scores on the CTQ and relatively lower measures of spontaneous recovery (Figure 6). Within the specified order of the analysis, scores on the CTQ will have the most predictive value for PTSD symptom severity.

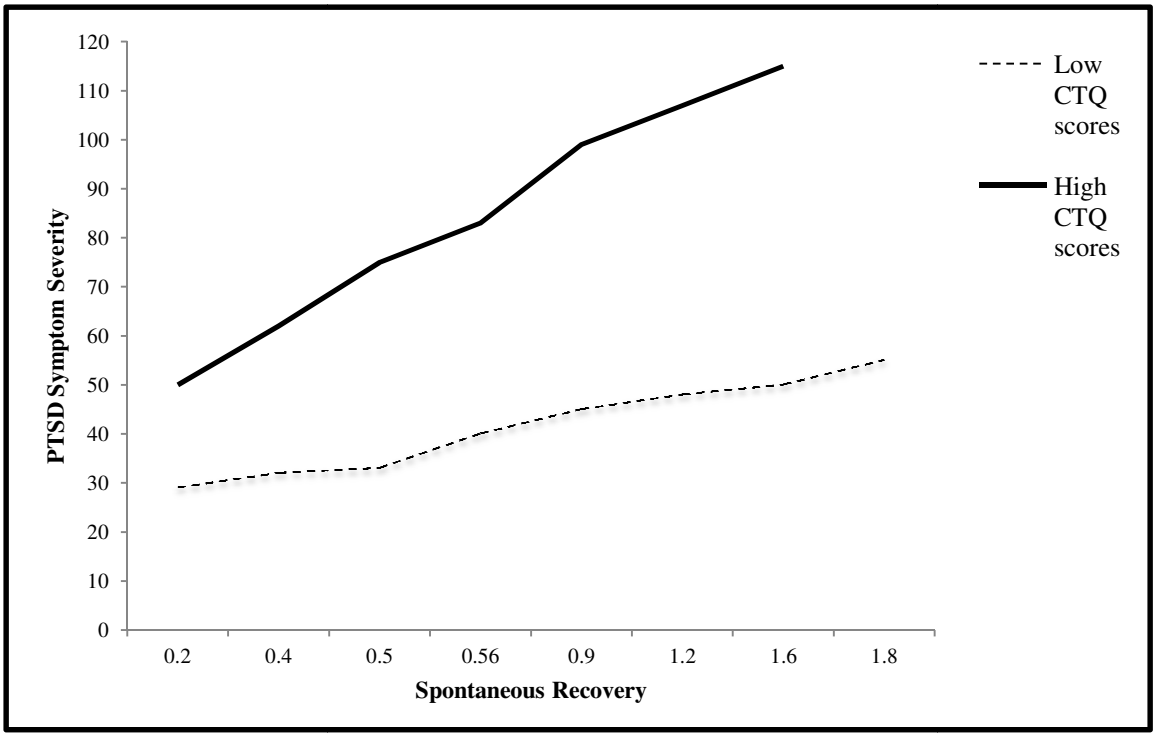


Figure 6. Individuals will be placed in the 'Low CTQ scores' group if they are in the bottom 50th percentile of the group, and individuals will be placed in the 'High CTQ scores' group if they are in the upper 50th percentile of the group. This graph reveals that individuals with high CTQ scores as well as high measures of spontaneous recovery are most susceptible to developing comparatively severe symptoms of PTSD.

Discussion

In this experimental proposal, the classical fear-conditioning paradigm will be implemented to assess the susceptibility of EMTs to developing symptoms of PTSD (e.g., hypervigilance, intrusion, and avoidance). Within the fear-conditioning paradigm, spontaneous recovery will be used to measure symptom severity through SCR, which is a valid psychophysiological tool to determine the presence and severity of a fear response (Schiller et al., 2009; Monfils, Cowansage, Klann & LeDoux; 2009). This experiment is novel in that it is the first study of its kind that proposes to use fear conditioning to study susceptibility to PTSD. Overall, results will indicate a main effect of spontaneous recovery, implying that it is an

efficient measure to assess susceptibility, as higher measures of spontaneous recovery will correlate with higher scores on the CAPS-V and inferentially, more severe PTSD symptoms.

The results of the statistical analysis will also reveal a main effect of scores on the CTQ. This implies that an individual that experiences traumatic calls as an EMT and has experiences with childhood trauma is more susceptible to developing symptoms of PTSD than an individual who experiences traumatic calls as an EMT but has not been exposed to trauma in childhood. This affirms the results of meta-analyses and genetic studies, which have shown that childhood trauma is a contributing factor to susceptibility towards developing PTSD (Berntsen, Johannessen, Thomsen, Bertelsen, Hoyle & Rubin, 2012; Hoge, Austin & Pollack, 2007; Ozer, Best, Lipsey & Weiss, 2003). The analysis should also reveal a main effect for the tally of traumatic calls maintained by the participants over 6 months. This result will confirm that susceptibility to developing symptoms of PTSD increases with repeated or increased exposure to trauma. An individual with a higher tally of traumatic calls is more susceptible than an individual who only experiences few or no traumatic calls. This predicted result reveals the potential problems inherently associated with emergency response professions and helps in understanding the effect that repeated exposure to trauma has on human behavior.

The results of the statistical analysis will also reveal that the number of extinction trials has a main effect such that the more trials it takes for an individual's SCR to return to baseline (during extinction training on Day 2 of Phase I), the more susceptible they are to developing symptoms of PTSD. This measure can be interpreted as how difficult or easy it is for an individual to inhibit an old association and engage in new learning (i.e., extinction training). Individuals who require a greater number of trials to extinguish the fear association will also record higher measures of spontaneous recovery and hence, higher scores on the CAPS-V. This

implies that although these individuals will be most exposed to the CS+ in the absence of an aversive stimulus (UCS), they will not be able to dampen their fear associations upon re-presentation of the CS+ on Day 3. This indicates that there is some inherent learning mechanism that also contributes to how susceptible an individual is to developing symptoms of PTSD.

The results of the hierarchical regression will reveal that the interaction between scores on the CTQ and measures of spontaneous recovery are optimal at predicting PTSD symptom severity. Individuals who score high on the CTQ and record a high measure of spontaneous recovery will be the most susceptible to developing symptoms of PTSD, as compared to those who reported relatively lower scores on the CTQ and did not record a high measure of spontaneous recovery. This finding will support the results of many developmental studies that focus on childhood trauma as the cause for PTSD in adulthood.

The results of this study will have the potential to greatly benefit the emergency response community as it will allow agencies to take precautionary measures for their most susceptible members by providing appropriate care and interventions when faced with the aftermath of a particularly traumatic call. Since the training required to become an EMT is lengthy and expensive, EMS education organizations can use the CTQ as a predictor to assess who might be at greater risk of developing PTSD when working as an EMT. Additionally, agencies can use the CTQ as a screening tool for accepting or rejecting new EMTs based on their own resources. The findings from this study will reveal that susceptibility to PTSD is influenced by many factors that interact with one another, and will clarify that repeated exposure to trauma causes a higher level of susceptibility to developing symptoms of the disorder.

Study II: Assessing the efficacy of reconsolidation-blockade in EMTs diagnosed with PTSD

Introduction

When clinicians treat EMTs who are diagnosed with PTSD, it is important for them to consider that the nature of emergency response requires EMTs to face similar and varied traumatic situations repeatedly, sometimes multiple instances on a single shift. Studying the symptoms of PTSD in EMTs can provide insight into how repeated exposure to trauma affects the neural, biological and behavioral aspects of their functioning. The inclusion of "Repeated or extreme indirect exposure to aversive details of the event(s), usually in the course of professional duties" (American Psychological Association, 2013) in the DSM-5 definition of PTSD stressors also targets the growing need to provide more relevant therapeutic interventions for emergency responders, who play an extremely important role in society as the first ones to provide medical and legal assistance to the community they serve.

Currently, the literature indicates that cognitive-behavioral therapy (CBT) is efficacious and widely used to combat the symptoms of intrusion, avoidance and hypervigilance that are caused by various types of traumatic incidents (Kar, 2011). However, nonresponse to CBT can be as high as 50% in some populations, dependent on factors such as nature of the population and comorbidity with other disorders (Kar, 2011). CBT has a lower rate of remission compared to Eye Movement Desensitization Reprocessing (EMDR) therapy and other supportive therapies, but is equally efficacious as exposure therapy (Mendes, Mello, Ventura, Passarela & Mari, 2008). However, CBT is based on identifying and modifying the observable behaviors that manifest as symptoms of PTSD, rather than targeting the cognitive mechanisms through which these symptoms present. Because PTSD can be understood as a disorder of fear conditioning, it would be beneficial for patients if they were able to modify the original fear memory trace in

order to eradicate associations made between the traumatic event (and triggers or remainders of the event) and a fear response.

The process of memory reconsolidation works as an update mechanism for better integration of information (Rodriguez-Ortiz et al., 2007). Reconsolidation is dependent on the reactivation of the traumatic memory/memories, which are re-integrated into the LTM within six hours of the reactivation (Schiller et al., 2009). However, behavioral and pharmacological interventions (such as extinction training or beta-blockers like anisomycin and propranolol) administered before the passing of this time period can alter the fear memory trace to the point where the associations between traumatic events and fear can be completely eliminated (Schiller et al., 2009; Lonergan, Olivera-Figueroa, Pitman & Brunet et al., 2011; Pitman, Milad, Igoe, Vangel, Orr, Tsareva, Gamache & Nader, 2011). This intervention is called reconsolidation-blockade as it prevents memories from becoming further reconsolidated in the LTM.

Under this premise, Study II aims to assess the efficacy of reconsolidation-blockade in EMTs who have been diagnosed with PTSD using a discrimination fear-conditioning paradigm. Similarly to Study I, Study II will make use of the measure of spontaneous recovery to determine whether reconsolidation-blockade is effective in reducing the electro-dermal arousal experienced in response to fear-related stimuli. Additionally, this experiment will look into whether reconsolidation-blockade is useful for general fear memory traces, or whether its efficacy extends to context-specific (EMS-relevant) stimuli as well.

Methods

One hundred EMT volunteers (21-60 years old, 50 female) will be recruited from various emergency response units in New York City, NY. All volunteers will have a current clinical diagnosis of mild-moderate PTSD. This diagnosis will be confirmed by administering the Clinician Administered PTSD Scale for DSM-V (CAPS-V) (overall Cronbach's α= 0.95). Volunteers that do not score higher than 45 on the CAPS-V will not be included in the study since this implies that they do meet the requirements for a clinical diagnosis of PTSD. None of the volunteers should report taking any medications to assist with PTSD symptoms and should not currently be seeking any behavioral therapeutic intervention. If participants begin any kind of treatment during the course of the study, their data will be excluded to avoid confounding effects of medication and therapy. Participants should not have any comorbid diagnoses. All participants will be cognizant of the details of the study in order to obtain informed consent, and the study will be submitted to the Institutional Review Board for human subject research at Bard College to receive approval. At the end of the experiment, reconsolidation-blockade will be incorporated into the therapeutic treatment of individuals should they seek it, in order to benefit from the ameliorative effects of this process on the symptoms of PTSD.

Procedure

On Day 1 of the study, a fear conditioning discrimination paradigm with partial reinforcement of shocks will be used to induce an acquired fear response to both context-specific (i.e., emergency response-related) stimuli and stimuli known to be evolutionarily fear-inducing (e.g., pictures of snakes and spiders). These threatening animal-related pictures are known to be phylogenetically relevant to inducing a fear response, which is thought to explain findings that fear responses are recognized more easily to them (Fox, Griggs & Mouchlianitis, 2007; Mallan,

Lipp & Cochrane, 2013; Purkis & Lipp, 2009). Additionally, given the relevance of emergency-response related images to participant's specific PTSD triggers, a similar facilitation may take place for the EMS-relevant stimuli. All participants will undergo a calibration procedure to determine a level of shock that is "highly irritating but not painful" by rating different intensities of shocks on a scale of zero (no sensation) to 10 (highly irritating but not painful) until they evaluate a particular intensity as 10. These intensities of shocks will be generated using the Coulbourn Transcutaneous Aversive Finger Stimulator (E13-22; designed for human research), which employs a 9-V dry cell battery attached to an adjustable step-up transformer. The skin conductance response (SCR) as well as electric shock calibration will be recorded using apparatus described in the SCR section. Prior to the experiment and using the established comfortable level of voltage, the baseline skin conductance of all participants will be measured for two minutes, in the absence of any stimulus. Any participant with SCR amplitude of less than 0.05 μSiemens will be excluded from the study as per protocol stated in Wood, Ver Hoef & Knight (2014).

On Day 1, all participants will be asked to sit in front of a computer screen placed 60 cm away from the face. Participants will view one hundred stimuli encompassing four pictures, presented at random (See Appendix for procedural details). Each participant will view twenty-five presentations of a context-specific picture, which will depict an emergency response scenario. Of these 25 presentations, 38% will be associated with a shock as per protocol stated in Schiller et al (2009). This picture will be called the Contextual Conditioned Stimulus + (CCS+). Participants will view twenty-five presentations of a picture of a snake. Of these 25 presentations, 38% will be associated with a shock as per protocol stated in Schiller et al (2009). This picture will be called the Non-contextual Conditioned Stimulus + (NCS+). The remaining

50 stimuli presentations will be equally divided between another context-specific (related to emergency response) and another non context-specific picture (picture of a spider). These will be called Contextual Conditioned Stimulus – (CCS-) and Non-contextual Conditioned Stimulus – (NCS-) respectively. The presentations of the CCS- and NCS- stimuli will not be associated with shocks at any point in the experiment. SCR will be measured for all trials. Any participants with SCR lower than their baseline in response to shocks will be excluded from the study due to the lack of observable fear acquisition.

Participants will be asked to return to the lab the next day. On Day 2, participants will be randomly assigned to one of two groups. One group will undergo behavioral reconsolidation-blockade (experimental group) and the other group will not experience any form of reconsolidation-blockade (control group). For the experimental group, the CCS+, CCS-, NCS+ and NCS- pictures will be shown once without the presence of the shock. This will serve to re-activate the memory trace from Day 1. To ensure that extinction occurs within the time frame previously shown to be effective for reconsolidation-blockade, participants will undergo extinction training ten minutes after reactivation (Schiller et al., 2009). Extinction training will conclude when the SCR of participants in the experimental group reaches baseline. Extinction training has shown to be efficacious as a means of reconsolidation-blockade when carried out at the optimum period of time (Schiller et al., 2009). The number of trials needed for the SCR to return to baseline will be recorded. Soeter & Kindt (2011) reported that behavioral reconsolidation-blockade is just as effective as pharmacological reconsolidation-blockade (using agents such as propranolol) and does not produce side effects like depression, hallucinations, confusion, psychosis, etc. (Griffin & Friedman, 1986; Levinson & Acquaviva, 1988) hence only a behavioral intervention will be used.

The control group will differ from the experimental group in that they will not be subject to reactivation of the fear memory trace. Instead of having an initial presentation of all four stimuli on Day 2 in the absence of shocks, the control group will only undergo extinction training at the same time and in the same fashion as the experimental group. Twenty-four hours after this, participants will be asked to return to the lab on Day 3. Both groups will be shown one presentation of the CCS+, CCS-, NCS+, NCS- pictures without any presence of shocks. SCR will be measured for this trial. For both experimental and control groups, and in response to each stimulus, spontaneous recovery will be measured as ((SCR from Day 3 – last trial of extinction on Day 2)) as per protocol stated in Schiller et al. (2009). This experimental timeline can be followed in Figure 7.

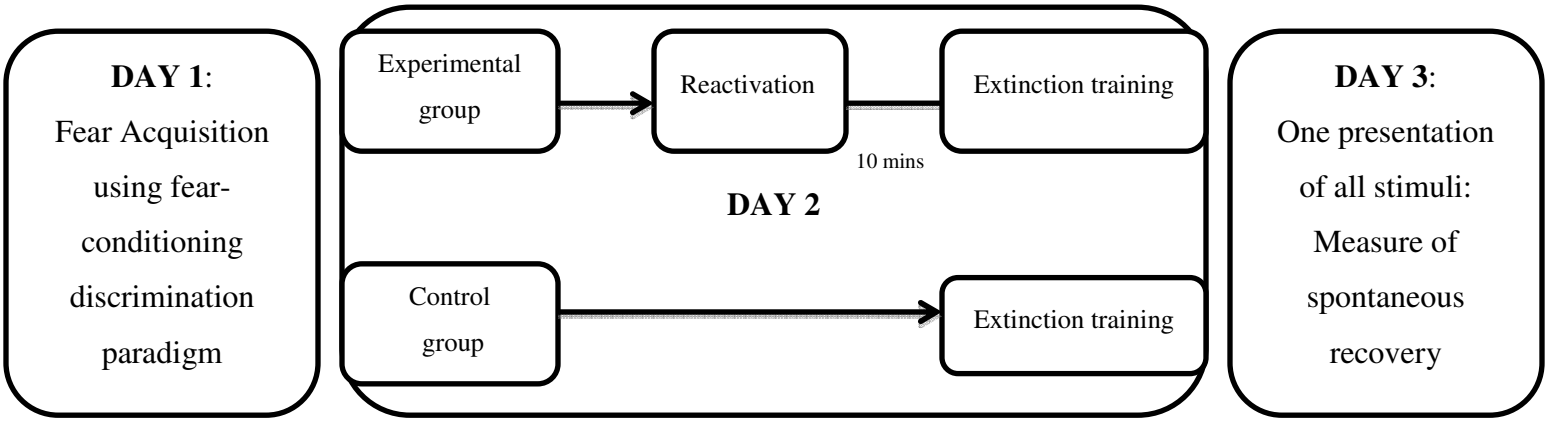


Figure 7. Timeline of events for Study II

Survey Measures

Clinician Administered PTSD Scale for DSM-V (CAPS-V)

The CAPS-V (Blake, Nagy, Kaloupek, Gusman, Charney & Keane, 1995) test will be administered to all participants at the beginning of the study to confirm the presence of PTSD and assess the severity of symptoms for individuals. CAPS-V is a 30-item structured clinical

interview that is effective in making a current or lifetime diagnosis of PTSD and can also assess PTSD symptoms experienced in the recent past. Questions target not only the duration of symptoms described in the DSM, but also subjective distress, impact of symptoms on social and occupational functioning, overall response validity, and overall PTSD severity. Inter-rater reliability for global severity correlation is 0.89 (Hovens, Van Der Ploeg, Klaarenbeek, Bramsen, Schreuder & Rivero, 1994). Overall Cronbach's alpha for CAPS-V is 0.94 (Blake et al., 1995).

Skin Conductance Ratings

SCR will be recorded using the Coulbourn Transcutaneous Aversive Finger Stimulator and Coulbourn Isolated Skin Conductance coupler (V71-23); 9mm (sensor diameter) Invivo Metric Ag/AgCl electrodes will be placed on the distal phalanx of the middle and ring fingers of the non-dominant hand as per protocol dictated in Fowles, Christie, Edelberg, Grings, Lykken, & Venables (1981). Electrodes will be placed 14 mm apart from each other. The Coulbourn Lablinc Analog to Digital converter (V19-16) will digitize the SC analog signal at 1000 Hz. All measurements of SCR will be recorded on a Mac-compatible computer and custom designed software provided by Coulbourn Instruments.

Statistical Analysis

All statistical analyses will be carried out with the Statistical package for the Social Sciences (SPSS) Version 21.0 for Mac (SPSS Inc., Chicago, Illinois). The dependent variable (DV) will be the measure of spontaneous recovery. The categorical independent variables (IV) will be the stimulus type (context-specific or non context-specific pictures) reinforcer type (shock or no shock), the condition type (reconsolidation-blockade or control group) and the continuous IV will be the score on the CAPS-V (to control for severity of symptoms between participants). A multiple regression analysis will model the main effects of reinforcer type,

stimulus type, and condition type. All 2-way interactions between categorical IVs will be assessed. A 3-way interaction will be used to analyze the effect of all three categorical IVs on the measure of spontaneous recovery.

Predicted Results

The results of the regression analysis will reveal a main effect for condition type (reconsolidation-blockade group or no reconsolidation-blockade group) such that the measures of spontaneous recovery for the group that underwent behavioral reconsolidation-blockade should be significantly lower than that of the control group. There will also be a main effect of stimulus type (context-specific vs. non context-specific stimuli), such that the measure of spontaneous recovery to non context-specific pictures should be significantly lower than to context-specific pictures. A main effect of reinforcer type (shock or no shock) will be observed such that stimuli that were paired with shocks (CCS+ and NCS+) on Day 1 of the discrimination fear-conditioning paradigm will elicit a significantly higher measure of spontaneous recovery than stimuli that were not associated with shocks at any point in the experiment (CCS- and NCS-).

Between the categorical IVs, there will also be significant 2-way interactions. The analysis will reveal a significant 2-way interaction between condition type and reinforcer type (Figure 8) such that the measure of spontaneous recovery will be higher for stimuli associated with shocks (CCS+ and NCS+) in the group that will not undergo reconsolidation-blockade as compared to the group that will undergo reconsolidation-blockade. There will be no significant difference between condition groups for stimuli that are not associated with shocks (CCS- and NCS-). There will be a significant 2-way interaction between reinforcer type x stimulus type (Figure 9), such that the measure of spontaneous recovery will be significantly higher in

response to the CCS stimuli, and measure of spontaneous recovery for stimuli associated with shock (CCS+ and NCS+) will be significantly higher than to stimuli not associated with shocks (CCS- and NCS-), implying that the CCS+ stimulus will elicit the highest measure of SR.

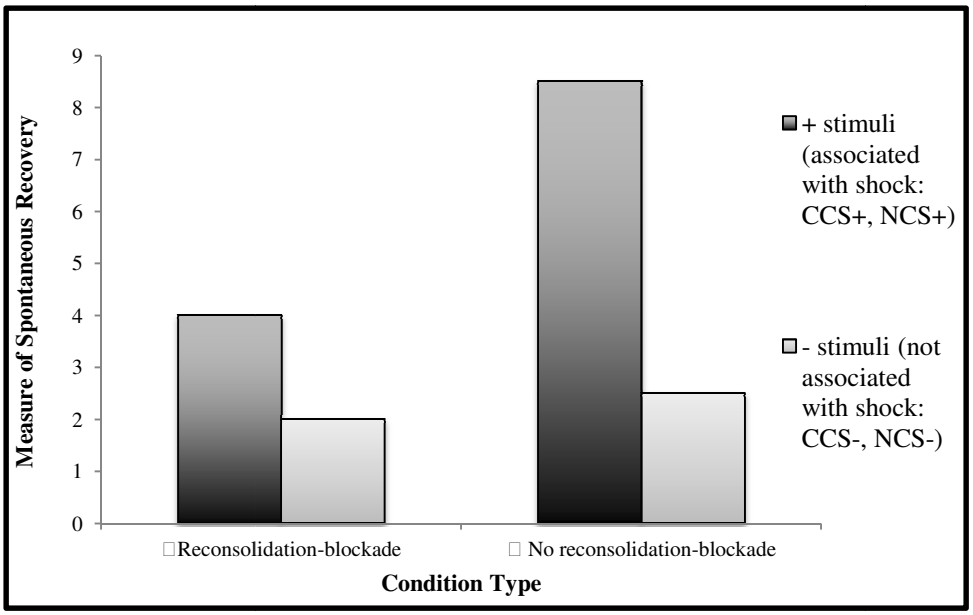


Figure 8. The response to CCS+ and NCS+ stimuli for individuals in the non reconsolidation-blockade group will elicit the highest measure of spontaneous recovery as compared to individuals in the consolidation group or responses to the CCS- and NCS- stimuli, indicating an interaction effect between reinforcer type (shock vs. no shock) and condition type (reconsolidation-blockade vs. no reconsolidation-blockade).

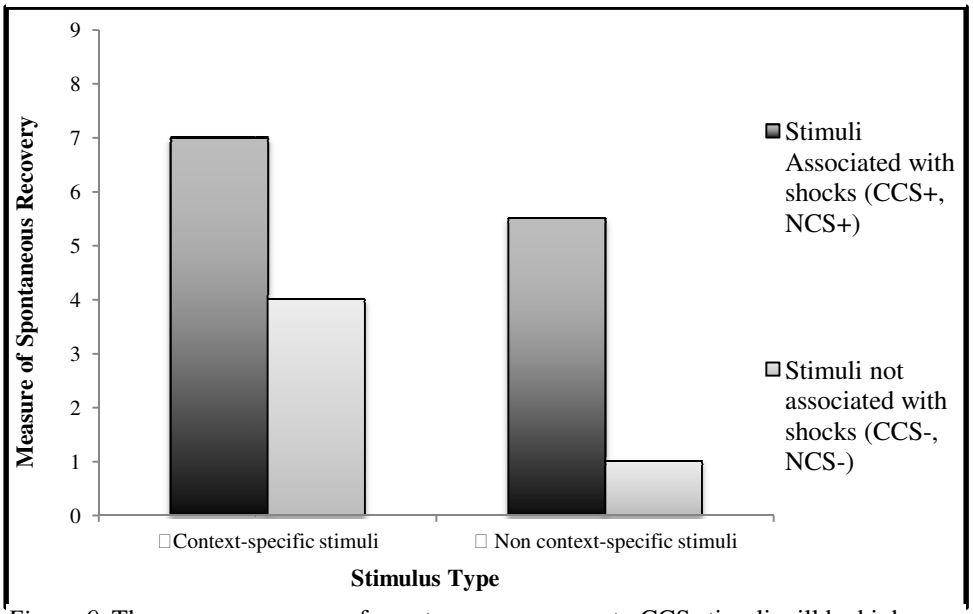
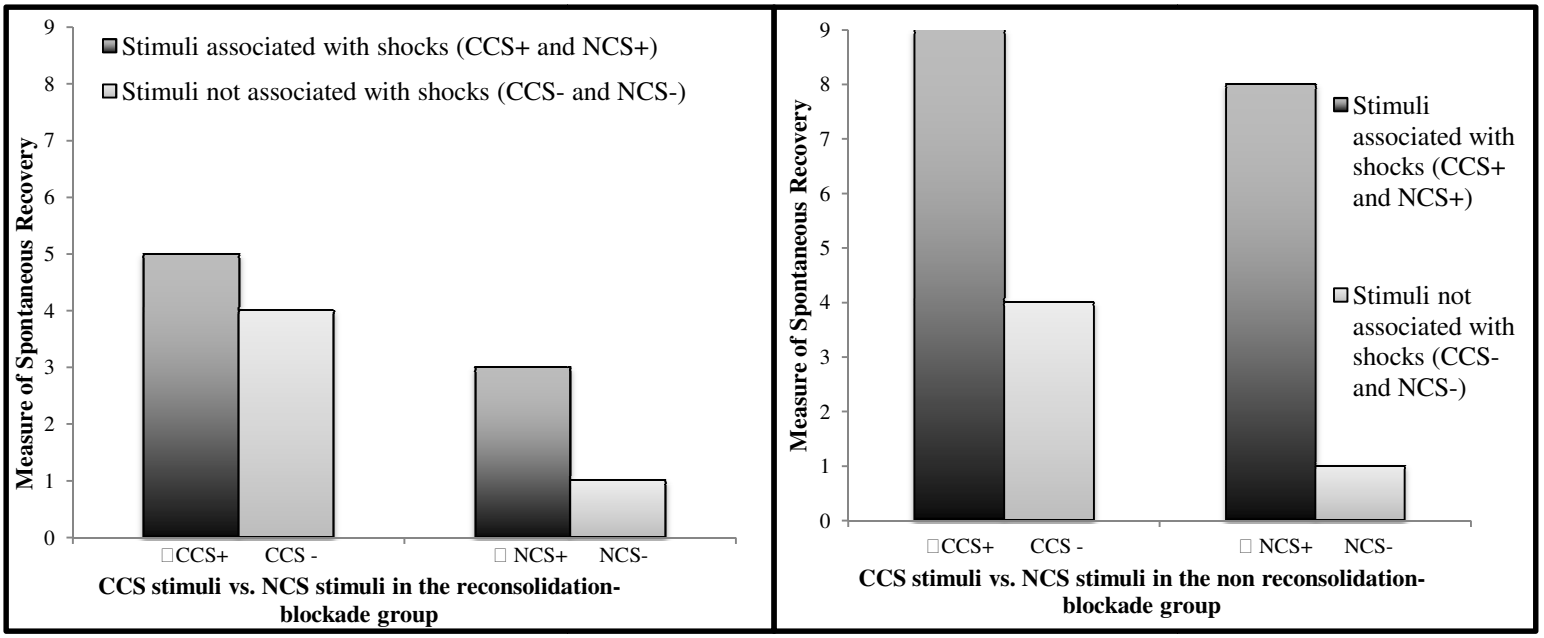


Figure 9. The average measure of spontaneous recovery to CCS stimuli will be higher than the average response to NCS stimuli. Overall, the response to stimuli associated with shocks (CCS+ and NCS+) will be higher than the response to stimuli not associated with shocks (CCS- and NCS-). This indicates an interaction effect between stimulus type (CCS vs. NCS) and reinforcer type (shock or no shock).

The results of the 3-way interaction will reveal that there is a statistically significant difference between the 2-way interaction of reinforcer and stimulus type at the level of the condition group (reconsolidation-blockade vs. no reconsolidation-blockade). For the group that will undergo reconsolidation-blockade, the measure of spontaneous recovery to the CCS+ stimuli will be significantly lower than the group that does not undergo reconsolidation-blockade. There will be no significant difference between conditions for the measures of spontaneous recovery to the CCS- stimuli. For the group that will undergo reconsolidation-blockade, the measure of spontaneous recovery to the NCS+ stimuli will be significantly lower than the group that will not undergo reconsolidation-blockade. There will be no significant difference between conditions for the measures of spontaneous recovery to the NCS- stimuli (Figures 10 and 11).



F*igures 10 and 11.* A 3-way interaction takes place at the level of condition type (reconsolidation-blockade vs. no reconsolidation-blockade) between reinforcer type (shock or no shock) and stimulus type (CCS or NCS stimuli). Individuals in the control group will have the overall highest measure of spontaneous recovery in response to the stimuli associated with shock (CCS+ > NCS+), as compared to the individuals in the experimental group.

Discussion

This experimental proposal was designed to assess the efficacy of behavioral reconsolidation-blockade in EMTs diagnosed with PTSD by implementing a fear-conditioning task that presented both general, evolutionarily fear-inducing stimuli (snakes and spiders) and EMS-relevant fear-inducing stimuli. The aim of including both types of stimuli will be to determine if behavioral reconsolidation-blockade can modify or eliminate fear memory traces that are relevant to EMS-related stimuli in the same way that it has shown to do for general fear memory traces (Nader et al., 2000; Steinfurth et al., 2014; Monfils et al., 2009).

There will be a main effect for stimulus type (context-specific vs. non context-specific), implying that the CCS+ stimulus will elicit a higher measure of spontaneous recovery than the NCS+ stimulus, and the CCS- stimulus will elicit a higher measure of spontaneous recovery than the NCS- stimulus. This can be attributed to the nature of the emergency response profession, wherein EMTs are likely to react more strongly to the presentation of a traumatic context-specific stimulus than to the presentation of a non context-specific, evolutionarily fear-inducing stimulus. This is most likely because EMTs are trained to be observant and attentive to emergency scenarios that depict people in medical distress. These pictures are not only relevant to the daily profession of the EMT, but they also serve as triggers for individual's PTSD symptoms. The contextual stimuli cause an increase in electro-dermal response that is comparatively higher than the response to non-contextual stimuli, which are only phylogenetically fearful and do not trigger PTSD symptoms.

The results of the significant 2-way interaction (reinforcer type x stimulus type) will indicate that the stimuli associated with shocks will elicit a significantly higher measure of spontaneous recovery than those that are not associated with shocks, and the CCS+ stimulus will

elicit a higher measure of spontaneous recovery than the NCS+ stimulus. Additionally, the SCR recorded in response to the CCS- stimulus will be higher than the SCR recorded in response to the NCS- stimulus (although this difference will not be significant). This will imply that overall, this population is prone to displaying a fear response to EMS-relevant stimuli regardless of whether it is associated with an aversive outcome, potentially because EMTs are trained to be alert when witnessing scenarios depicting emergency response.

There will also be a significant 2-way interaction between condition type and reinforcer type. This indicates that in the control group, the measure of spontaneous recovery in response to stimuli associated with shocks (CCS+ and NCS+) will be highest. While reconsolidation-blockade will be effective at ameliorating the fear response for both CCS+ and NCS+ stimuli, the SCR in response to the NCS+ stimuli will be lower than to the CCS+ stimuli. The interaction also reveals that the overall measure of spontaneous recovery to CCS stimuli will be higher than the measure of spontaneous recovery to NCS stimuli. This implies that reconsolidation-blockade will be effective at ameliorating the symptoms of hypervigilance and electro-dermal arousal that arise form PTSD, but it will not be able to overcome the inherent response of the EMT to react with alertness to CCS stimuli. This can be attributed to the baseline level of arousal that persists in EMTs upon viewing an emergency scenario.

The results of the 3-way interaction will imply that while reconsolidation-blockade is overall effective at ameliorating the fear memory trace for both evolutionarily fear-inducing and EMS-relevant stimuli, it is more effective for non context-specific stimuli. This is due to the baseline level of arousal that presents itself when an EMT views an emergency scenario, as well as the arousal experienced when viewing PTSD triggers. So while reconsolidation-blockade might help EMTs to overcome the learned fear response associated with the CCS+ stimulus,

their training and instincts override this to elicit some amount of arousal even after reconsolidation has been successfully blocked. Reconsolidation-blockade will not significantly affect the measures of spontaneous recovery in response to stimuli not associated with shocks (CCS- and NCS-), but the CCS- picture will still elicit a higher measure of spontaneous recovery than the NCS- picture due to the content of the stimulus.

The results of Study II indicate that reconsolidation-blockade will be effective at ameliorating the learned fear responses to both non-contextual, evolutionarily fear-inducing stimuli and contextual, EMS-relevant stimuli for individuals in the experimental group, as measured by a lower measure of spontaneous recovery compared to individuals in the control group. However, reconsolidation-blockade does not inhibit the inherent arousal and alertness experienced by EMTs upon viewing pictures of people in medical distress. This is attributable to their training, which teaches them to remain alert and vigilant during emergency calls. Hence, reconsolidation-blockade can be a beneficial addition to pre-existing therapeutic methods such as exposure therapy, as it has the potential to eliminate fear memory traces and associations in EMTs without affecting the baseline arousal needed for them to remain alert on duty.

Conclusion

PTSD is a disease of fear acquisition towards a specific stimulus, and manifests itself in the symptoms of intrusion, hypervigilance and avoidance. These symptoms cause significant functional impairment in the lives of patients (Rodriguez, Holowka & Marx, 2012; Westphal, Olfson, Gameroff, Wickramaratne, Pilowsky, Neugebauer, Lantigua, Shea & Neria, 2011) and the key to ameliorating them is by modifying the memory trace that the fear-inducing stimulus elicits. Individuals in the profession of emergency response must also face the problem of being repeatedly exposed to traumatic incidents. Even one traumatic incident has shown to alter neural circuits in the brain that are involved with the stress response (Bremner, 2006; Villarreal & King, 2004; Olff, Langeland & Gersons, 2005). Thus, repeated exposure to trauma places individuals such as EMTs at an even greater risk of developing stress-related disorders. These experimental proposals aim to explore the role that repeated exposure to trauma has on behavioral aspects of arousal.

The first experiment is a longitudinal study structured around individual susceptibility to developing symptoms of PTSD. By implementing a generalized fear-conditioning task, spontaneous recovery can be assessed using SCR, which is a valid measure of arousal and fear. The hypothesis is that a higher measure of spontaneous recovery in an individual renders them more susceptible to developing symptoms of PTSD if they choose to work in the emergency response profession. This hypothesis will be tested by comparing individuals' measures of spontaneous recovery to their scores on the Clinician Administered PTSD Scale for DSM-V (CAPS-V). Individuals with higher CAPS-V scores will also have higher measures of spontaneous recovery, confirming the hypothesis and validating spontaneous recovery as an appropriate measure to assess susceptibility to PTSD. In addition to this, the CAPS-V scores and

measures of spontaneous recovery will be entered into a hierarchical regression analysis to control for the effect of other known factors that increase susceptibility to PTSD, such as childhood trauma, tally of traumatic calls and number of trials needed for extinction training to successfully bring the SCR back to baseline. This will help to provide a thorough understanding of the factors that would impact an individual intending to join the emergency response profession.

The predicted results of the first experimental proposal regarding the susceptibility of EMTs can be used to determine if an individual from the normative population would be at risk for developing PTSD upon choosing to join the profession. Emergency response agencies can supply applicants and members with easily available questionnaires that assess childhood trauma (such as the CTQ), and the impact of any current traumatic experience, and use these results to determine if certain members are more susceptible to developing PTSD than others. Unfortunately, one limitation of this proposal is that it is difficult to accurately assess spontaneous recovery outside the lab, without the use of SCR devices. However, it is conceivable that future research could result in the production of a trauma questionnaire or scale that could positively correlate with the measure of spontaneous recovery and provide insight into whether an individual might be susceptible to PTSD, without the direct use of SCR.

Another limitation of the first proposal is that the predicted results might not match real results, rendering spontaneous recovery an ineffective tool to compare with PTSD symptom severity. Zohar et al. (2011) characterize PTSD as a disorder where the normal response to a traumatic incident fails to disappear. While the normative population may experience symptoms of hypervigilance, intrusion and avoidance after a traumatic experience, this is considered a normal response. However, the DSM-5 allows for the diagnosis of PTSD only if these symptoms

persist for longer than a month, implying that the key to understanding PTSD is not the response itself, but the duration.

Kearns, Ressler, Zatzick & Rothbaum (2012) also support the claim that the failure of extinction leads to the development of PTSD. Fear conditioning paradigms applied to animal models have also shown evidence of spontaneous recovery in subjects that indicates the return of fear to a conditioned stimulus in the absence of the aversive stimulus (Schiller et al., 2009; Monfils, Cowansage, Klann & LeDoux; 2009). The failure to recover from the normal response, and instead experience the traumatic association repeatedly can be characterized as spontaneous recovery, providing credibility for Study I's predicted results and inferentially, for using spontaneous recovery to study PTSD symptom severity.

If further pilot testing can establish spontaneous recovery as a valid tool to assess PTSD symptom severity, future studies could potentially use it to determine whether the pattern of response is similar or varied between PTSD patients who have been repeatedly exposed to trauma and those who have developed PTSD from a single traumatic incident. Testing of this nature has the potential to reveal information not only about the effects that repeated exposure to trauma has on the behavior of an individual, but it could also advance our understanding of the human fear response. Although the measure of spontaneous recovery is most helpful in assessing the symptom of intrusion, it is also indicative of why certain triggers might be persistently avoided or why they might induce states of hypervigilance in individuals. In order to target these two symptoms, future studies could modify the protocols described for Study II and provide a comprehensive view of approaching all symptoms of PTSD through fear conditioning.

Although providing a framework to understand what factors affect the susceptibility of EMTs to developing PTSD is extremely relevant for helping individuals make educated choices

about their profession and in helping susceptible individuals take appropriate measures to avoid the disorder, the emergency response profession has already contributed to the development of PTSD in many members, making EMS a risky profession for susceptible individuals. As PTSD is a disorder of traumatic memories, the second experimental proposal focuses on the cognitive aspect of treatment through the lens of fear conditioning. By targeting the neural circuits that produce the behavioral symptoms rather than simply modify the observable pattern of behaviors and emotions, the second experiment attempts to modify associations made to traumatic memories in order to create a long-lasting change in patients.

The second experiment is structured around assessing the efficacy of reconsolidation-blockade in EMTs who have been diagnosed with mild-moderate PTSD. It also aims to determine if reconsolidation-blockade is efficacious at ameliorating the fear response (increased arousal in the form of SCR) when it is associated with EMS-relevant stimuli (pictures of emergency scenarios depicting people in distress), since it is situations of emergency response that cause PTSD in this population. The hypothesis is that reconsolidation-blockade will be effective at ameliorating the fear response that is acquired to both evolutionarily fear-inducing and EMS-relevant stimuli. This will also imply that reconsolidation-blockade is particularly useful for including in the treatment of an individual who has been repeatedly exposed to traumatic events.

The design of the second experimental proposal poses a problem with regard to the stimuli presented to participants. The pictures used for context-specific stimuli (CCS+ and CCS-) are intended to depict emergency response scenarios, but are also chosen for their ambiguity regarding the nature of the emergency scene. Participants might attribute their PTSD symptoms only to a particular type of call, which might not be depicted in either of the context-specific

stimuli. This might lead to the absence of a significant difference in responses to the context-specific stimuli versus the non context-specific stimuli, which would make it difficult to assess whether reconsolidation-blockade is efficacious against context-specific stimuli (since the stimuli would not be related to the cause of the participant's PTSD). A potential solution to this problem could be to investigate the nature of the call/s that caused PTSD for each individual, and then create stimuli to reflect the same. This would also imply that all stimuli would have be to counter-balanced for valence in order to ensure that all participants will be subjected to stimuli of similar intensity.

There is also some ambiguity regarding the predicted response of EMTs to the context-specific and non context-specific stimuli. This experiment hypothesizes that in comparison to the non context-specific stimuli, EMTs will have an overall higher SCR to context-specific stimuli, not only because they are primed to react with alertness to scenarios depicting people in medical distress, but also because these pictures serve as a trigger for their own PTSD. Reconsolidation-blockade is predicted to ameliorate the fear response that arises from having PTSD, but is not expected to diminish the inherent arousal experienced by EMTs upon viewing the CCS stimuli. However, depending on the number of years an EMT has served and their potential desensitization to stimuli depicting emergency scenarios, their reaction to the non context-specific, evolutionarily fear-inducing stimuli might be greater than their response to context-specific stimuli. This problem might be resolved if stimuli were more personalized to reflect individual causes of PTSD since they would be more likely to cause a greater level of arousal.

The implications of this study are extremely beneficial for treating EMTs who have been diagnosed with PTSD, especially if their PTSD is associated with the nature of their profession. By adapting the window of reconsolidation into treatments that are based on extinction training

(such as exposure therapy), it is possible to modify the memory traces that are associated with their fear response. This increases the efficacy of the treatment by targeting the heart of the disorder, and also ensures for a long-lasting change.

These two experimental proposals aim to create a profile of how PTSD operates in humans using fear conditioning as the basis for understanding and treating the disorder. Although both proposals include the use of SCR to assess the fear response, future studies can use these predicted results as pilot tests to create an extensive behavioral analysis of the fear response using other measures such as startle reflex, heart rate and blood pressure. Additionally, both these studies target only the behavioral aspect of PTSD, but do not delve much into the neural or chemical changes that occur simultaneously. Using event related potentials (ERPs) and functional magnetic resonance imaging (fMRI) technology; it is possible to gain further insight into the neurochemical changes caused by PTSD.

PTSD research has already identified the key areas of the brain that are involved in the processing of trauma and are hence, greatly affected by the development of PTSD. The nature of trauma has multiple effects on the neurochemistry of the brain and subsequently, on human behavior as well. On the endocrine level, the hypothalamic-pituitary-adrenal (HPA) axis is responsible for regulating the stress response. The hypothalamus releases Corticotropin Releasing Factor (CRF), which in turn stimulates the production of adrenocorticotropic hormone (ACTH) from the pituitary gland (Bremner, 2006). The final step in this reaction causes the adrenal gland to produce cortisol, the hormone that helps mediate the fight-or-flight response (Bremner, 2006) when an individual faces a fearful/unsafe situation. On the neural level, cortisol and norepinephrine levels fluctuate in the amygdala, medial prefrontal cortex, and hippocampus as part of the stress response (Bremner, 2006). The amygdala plays a role in emotion regulation

(Cacioppo et al., 2013); the medial prefrontal cortex (PFC) regulates decision-making and judgment (Cacioppo et al., 2013) and the hippocampus is involved in the various processes that convert information into memories (Cacioppo et al., 2013).

These three brain regions have been identified as being involved in the processing of trauma (Bremner, 2006) but they also play an important role in the functioning of verbal declarative memory (Elzinga & Bremner, 2002). Because of their involvement in normative functioning, PTSD patients often suffer from verbal declarative memory deficits as the amygdala, medial PFC and hippocampus undergo anatomical and neurotransmitter changes (Elzinga & Bremner, 2002). As compared to the normative population, PTSD patients have shown deficits in hippocampal activation on a verbal declarative memory task (Yehuda, Golier, Tischler, Harvey, Newmark, Yang & Buchsbaum, 2007). PTSD did not alter the visual declarative memory in patients (Bremner, 2006), implying that the witnessing of the traumatic incident (as compared to merely hearing about a traumatic incident) plays a role in contributing to symptoms of the disorder, especially intrusive thoughts, spontaneous re-experiencing and flashbacks.

An especially interesting change that takes place in the neural circuits of patients with PTSD is the increased amygdalar function accompanied by decreased medial prefrontal function upon viewing traumatic reminders (Shin, Orr, Carson, Rauch, Macklin, Lasko, Peters, Metzger, Dougherty, Cannistraro, Alpert, Fischman & Pitman, 2004). This finding indicates that the medial prefrontal cortex is unable to modulate or inhibit the emotional dysregulation caused by the amygdala, which could account for the observable increase in PTSD symptoms upon viewing of traumatic reminders (Shin et al., 2004). There is also dysregulation of the HPA axis in PTSD, wherein individuals with chronic PTSD are found to have lower levels of cortisol and higher

levels of CRF. This confirms that PTSD causes a long-lasting stress response during which individuals are in a constant state of hypervigilance, and hence have an imbalance of the hormones and neurotransmitters usually released in response to stress.

Using what we already know about the changes that occur in the brain and the endocrine system during PTSD, questionnaires and tasks that assess cognitive capacity as well as ERPs and fMRI technology can be employed to track the neurochemical and cognitive changes elicited by the disorder to support the results of behavioral analyses. Although the field of trauma research is lacking in information about the effects of repeated exposure to trauma, the proposed experiments can pave the way to understanding how PTSD alters the behaviors of affected individuals, and can help establish an empirically sound method of treating individuals in the emergency response profession.

Additionally, the results of these experiments can be extended to other professionals in the field of emergency response, such as firefighters and police officers, who are also likely to encounter multiple PTEs due to the nature of their jobs. Hence, they too might present similar behavioral and neurochemical patterns in the face of repeated exposure to trauma. Research that focuses on better treatment options for EMTs, police officers and firefighters diagnosed with PTSD will help to improve the quality of their lives, which in turn will result in the optimal provision of care for the communities they serve.

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Appendix

Diagnostic and Statistical Manual of Mental Disorders (DSM)-V Definition of PTSD

Criterion A: stressor

The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, as follows: (one required)

1. Direct exposure.
2. Witnessing, in person.
3. Indirectly, by learning that a close relative or close friend was exposed to trauma. If the event involved actual or threatened death, it must have been violent or accidental.
4. Repeated or extreme indirect exposure to aversive details of the event(s), usually in the course of professional duties (e.g., first responders, collecting body parts; professionals repeatedly exposed to details of child abuse). This does not include indirect non-professional exposure through electronic media, television, movies, or pictures.

Criterion B: intrusion symptoms

The traumatic event is persistently re-experienced in the following way(s): (one required)

1. Recurrent, involuntary, and intrusive memories. Note: Children older than six may express this symptom in repetitive play.
2. Traumatic nightmares. Note: Children may have frightening dreams without content related to the trauma(s).
3. Dissociative reactions (e.g., flashbacks) which may occur on a continuum from brief episodes to complete loss of consciousness. Note: Children may reenact the event in play.
4. Intense or prolonged distress after exposure to traumatic reminders.

5. Marked physiologic reactivity after exposure to trauma-related stimuli.

Criterion C: avoidance

Persistent effortful avoidance of distressing trauma-related stimuli after the event: (one required)

1. Trauma-related thoughts or feelings.
2. Trauma-related external reminders (e.g., people, places, conversations, activities, objects, or situations).

Criterion D: negative alterations in cognitions and mood

Negative alterations in cognitions and mood that began or worsened after the traumatic event: (two required)

1. Inability to recall key features of the traumatic event (usually dissociative amnesia; not due to head injury, alcohol, or drugs).
2. Persistent (and often distorted) negative beliefs and expectations about oneself or the world (e.g., "I am bad," "The world is completely dangerous").
3. Persistent distorted blame of self or others for causing the traumatic event or for resulting consequences.
4. Persistent negative trauma-related emotions (e.g., fear, horror, anger, guilt, or shame).
5. Markedly diminished interest in (pre-traumatic) significant activities.
6. Feeling alienated from others (e.g., detachment or estrangement).
7. Constricted affect: persistent inability to experience positive emotions.

Criterion E: alterations in arousal and reactivity

Trauma-related alterations in arousal and reactivity that began or worsened after the traumatic event: (two required)

1. Irritable or aggressive behavior

2. Self-destructive or reckless behavior
3. Hypervigilance
4. Exaggerated startle response
5. Problems in concentration
6. Sleep disturbance

Criterion F: duration

Persistence of symptoms (in Criteria B, C, D, and E) for more than one month.

Criterion G: functional significance

Significant symptom-related distress or functional impairment (e.g., social, occupational).

Criterion H: exclusion

Disturbance is not due to medication, substance use, or other illness.

Specify if: With dissociative symptoms.

In addition to meeting criteria for diagnosis, an individual experiences high levels of either of the following in reaction to trauma-related stimuli:

1. Depersonalization: experience of being an outside observer of or detached from oneself (e.g., feeling as if "this is not happening to me" or one were in a dream).
2. Derealization: experience of unreality, distance, or distortion (e.g., "things are not real").

Specify if: With delayed expression.

Full diagnosis is not met until at least six months after the trauma(s), although onset of symptoms may occur immediately.

Study I: EMT Susceptibility to PTSD Symptoms

Consent Form

You are being asked to partake in a study conducted at Bard College, NY that aims to explore the susceptibility of newly trained Emergency Medical Technicians-Critical Care (EMT-CC) to developing symptoms of PTSD using a discrimination fear-conditioning task. The psychology program at Bard College is sponsoring this study.

This is a longitudinal study. Phase I of the study requests you to be in the lab every day for the next 3 days to complete the fear-conditioning task. Phase II of the study will occur 6 months after the conclusion of Phase I. You will receive contact from the investigators asking you to come back into the lab for a day of testing for Phase II. During the 6-month time period, you will be asked to record the number of traumatic EMS calls you responded to. You will be provided with a comprehensive definition of 'traumatic' call and a detailed set of instructions for how to maintain a tally from the investigators on the last day of Phase I.

Why is this study being done?
This study is being conducted to determine the susceptibility of EMTs to developing PTSD after being in the field for 6 months. This study will also consider other known factors that affect susceptibility to developing PTSD as an EMT.

What does this study involve?
The primary measure used in this study will be skin conductance response (SCR), which is the electro-dermal activity of the skin measured by electrodes placed on various points on the hand. Day 1 of Phase I involves purposefully acquiring fear to a certain stimulus by pairing it with mild shocks. A level of pain will be established by calibrating shocks prior to the task by asking you to determine a level of shock that feels "highly irritating but not painful". On Day 2 of Phase I you will be exposed to the same stimuli, but in the absence of shocks. On Day 3 of Phase I, you will be exposed to one final presentation of the stimuli in the absence of shocks, and you will also be asked to fill out two questionnaires—the Davidson Trauma Scale and the Childhood Trauma Questionnaire. You can choose to stop participating at any point in the experiment. If you choose to stop participating in the study during the 6 months after Phase I, please inform the researcher.

During Phase II, you will be shown the stimuli again and your SCR will be recorded in response to viewing the pictures. Additionally, you will also undergo a structured clinical interview with a mental health professional to determine your score on the Clinician-Administered PTSD scale for DSM-V (CAPS-V). This will be done to establish the presence and severity of PTSD symptoms.

How long will the study take?
Day 1 of Phase I will take approximately 2 hours and Day 2 and 3 will take approximately 1 hour each. Phase II, which only involves one day of testing will take approximately 1 hour. If you choose to end your participation in the experiment, all of your information and responses will be deleted.

What are the risks of this study?

This study does involve mildly shocking participants in order to acquire fear to a neutral stimulus. However, there are no health risks associated with the study, as shocks will be calibrated prior to the fear-conditioning task to ensure that individuals are shocked at a frequency that is 'highly irritating but not painful' to them. In order to protect your confidentiality, all the data collected will be kept on password-protected computers, which will only be accessible to the investigators of the project. An arbitrary subject number, the key to which will be stored separately from the data, will code your data. We will collect your name and email address for accounting purposes. This information will never be connected to your study data. The key that connects your subject ID to your identifying information will be destroyed at the end of Phase II.

What are the benefits of taking part in this study?

You will be paid $7 for every hour spent in the laboratory. Additionally, the data you provide will help the investigators understand the nature of repeated exposure to trauma and the factors that make EMTs susceptible to developing PTSD.

Whom do I contact if I have questions?

Any questions at any point in time during the study, or in between phases, can be directed to the primary investigator, Mythili Ananthasayan (m4487@bard.edu).

STATEMENT OF CONSENT

"I have understood the purposes of this study and the procedures involved with the experiment have been explained to me, as well as the associated risks and benefits. I have had the opportunity to ask questions and they have been answered to my satisfaction. I have also been informed of whom to contact in case I have more questions. I understand that I have the option of withdrawing at any point in time in the study. I have fully read this consent form and agree to participate in this study".

Name _____Date _____

Study I: EMT Susceptibility to PTSD Symptoms

Debriefing Form

Thank you for your participation!
In this study, the investigator was interested in knowing whether a classical fear-conditioning paradigm (specifically, the measure of spontaneous recovery to a previously learned and subsequently extinguished fear response) could accurately predict the susceptibility of newly trained EMT-CCs to developing symptoms of Post-Traumatic Stress Disorder (PTSD) in their first 6 months of being on duty. Previous research has shown that susceptibility to developing PTSD is influenced by the number of exposures to potentially traumatic events, presence/severity of childhood trauma and the concurrent responses to traumatic incidents that are presently affecting individuals. These factors, along with the number of trials it took for individuals to extinguish their learned fear response, were considered in the analysis.

Your participation in this study will help the investigator understand how fear conditioning can be used to study susceptibility to developing symptoms of PTSD. It will also help in understanding how PTSD affects a cohort that is repeatedly exposed to potentially traumatic events.

If you experienced any physical or psychological stress from being in this study, or specifically from being shocked as part of the experiment, please reach out to your squad's chief, established mental health provider or the nearest hospital to receive counseling. You can enter information about your location on this website to determine the nearest medical facility that can assist you: http://www.va.gov/directory/guide/division.asp?dnum=1&isFlash=0

If you have any additional questions or concerns, or would like to know the results of the experiment, please feel free to email Mythili Ananthasayan at ms4487@bard.edu.

If you would like to learn more about fear conditioning, PTSD or susceptibility factors, below are some links to background information and similar experiments that were used as a basis for this study.

http://www.psych.nyu.edu/phelpslab/files/Schiller_nature.pdf- fear-conditioning paradigm

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3513376/ - susceptibility and resilience factors in animal models

http://www.ptsd.va.gov/professional/PTSD-overview/dsm5_criteria_ptsd.asp- DSM-V criteria for the clinical diagnosis of PTSD

Study I: EMT Susceptibility to PTSD Symptoms

Timeline

1. Recruitment of participants- 2 months
Use this time to visit various medical emergency response agencies in New York City that offer EMT-CC training classes and recruit newly certified students to enroll in the study

2. PHASE I- Day 1
Participants will arrive at the lab. They will calibrate the level of shock that feels "highly irritating but not painful" to them. Participants will be hooked up to SCR recording instruments, and the fear-conditioning task will commence, which involves showing each participant 20 presentations of 2 stimuli.

3.PHASE I-Day 2
Participants will come back to the lab, and will be shown multiple presentations of both stimuli while being hooked up to SCR recording instruments, but in the absence of shocks. Stimuli will be shown until the SCR to the CS+ stimuli returns to baseline. The number of extinction trials needed to extinguish the fear response will be recorded.

4.PHASE I-Day 3
Participants will come back to the lab, and will be shown one presentation of both stimuli while being hooked up to SCR recording devices in the absence of shocks.

5. Next 6 months
Participants will be asked to keep a tally of all the traumatic calls they responded to. Participants will be instructed to follow the DSM-V criteria for 'stressor' (Criterion A) to have a reference for what is considered 'traumatic' but will be allowed to interpret and tally calls subjectively (e.g. a call might not be deemed traumatic by the DSM-V definition but might be considered traumatic by the individual participant, in which case it would count as a traumatic call).

6.Longitudinal follow-up-PHASE II
Participants will be given advance notice to come back to the lab 6 months after the completion of Phase I. Phase II will only consist of one day of testing, during which time participants will undergo a structured clinical interview using the CAPS-V to determine presence/severity of PTSD symptoms.

Study I: EMT Susceptibility to PTSD Symptoms

Predicted Budget

1. Skin Conductance Measuring System
    - MP150 acquisition system……..≈ $5,300
    - GSR amplifier……≈ $600
    - Electrode gel for GSR electrodes……..≈ $30
    - Transcutaneous Aversive Finger Stimulator……≈ $75
    - Isolated Skin Conductance coupler……..≈ $75
    - Disposable Ag/AgCl electrodes……..≈ $160
    - **TOTAL**……**≈ $6,165**

2. Standard Subject Participation Fees
    - (100 participants * ≈5 hours * $7)……..**≈ $3,500**

3. Assessment Tools
    - Childhood Trauma Questionnaire……..≈ $168
    - Clinician Administered PTSD Scale for DSM-5……available to clinicians/graduate students upon requesting the National Center for PTSD
    - Davidson Trauma Scale……..≈ $250
    - **TOTAL**……..**≈ $ 418**

GRAND TOTAL= $6,165 + $3,500 + $418 = **$10, 083**

Study II: Assessing the efficacy of reconsolidation-blockade in EMTs diagnosed with PTSD

Consent Form

You are being asked to partake in a study conducted at Bard College, NY that aims to explore the efficacy of a cognitive process called reconsolidation-blockade in the treatment of Post-Traumatic Stress Disorder in diagnosed Emergency Medical Technicians. The psychology program at Bard College is sponsoring this study.

Before beginning the study, you will undergo an interview with a certified clinician to determine the presence and severity of PTSD using the Clinician Administered PTSD Scale for the DSM-V (CAPS-V). This study involves a fear-conditioning task that takes places over the next 3 days.

Why is this study being done?
This study is being conducted to determine if reconsolidation-blockade can effectively ameliorate the fear-response that will be learned on Day 1 of the experiment. It also aims to assess the efficacy of reconsolidation-blockade against contextual stimuli (EMS-related) versus non-contextual stimuli.

What does this study involve?
The primary measure used in this study will be skin conductance response (SCR), which is the electro-dermal activity of the skin measured by electrodes placed on various points on the hand. Day 1 involves purposefully acquiring fear to certain stimuli by pairing them with mild shocks. A level of pain will be established by calibrating shocks prior to the task by asking you to determine a level of shock that feels "highly irritating but not painful". On Day 2 you will be placed in one of two groups by random assignment. Both groups will be exposed to all stimuli again, but in the absence of shocks. On Day 3, all participants will be exposed to one final presentation of all stimuli in the absence of shocks. You can choose to stop participating at any point in the study.

How long will the study take?
Day 1 will take approximately 2 hours and Day 2 and 3 will take approximately 1 hour each. If you choose to end your participation in the experiment, all of your information and responses will be deleted.

What are the risks of this study?

This study involves mildly shocking participants in order to acquire fear to a neutral stimulus. However, there are no health risks associated with the study, as shocks will be calibrated prior to the fear-conditioning task to ensure that individuals are shocked at a frequency that is 'highly irritating but not painful' to them. In order to protect your confidentiality, all the data collected will be kept only on password-protected computers, which will only be accessible to the investigators of the project. An arbitrary subject number, the key to which will be stored separately from the data, will code your data. We will collect your name and email address for accounting purposes. This information will never be connected to your study data. The key that connects your subject ID to your identifying information will be destroyed at the end of Day 3.

What are the benefits of taking part in this study?

You will be paid $7 for every hour spent in the lab. Additionally the data you provide will help the investigators understand the nature of repeated exposure to trauma and the efficacy of reconsolidation-blockade against PTSD that arises from working in the emergency response profession.

Whom do I contact if I have questions?

Any questions at any point in time during the study can be directed to the primary investigator, Mythili Ananthasayan (m4487@bard.edu).

STATEMENT OF CONSENT

"I have understood the purposes of this study and the procedures involved with the experiment have been explained to me, as well as the associated risks and benefits. I have had the opportunity to ask questions and they have been answered to my satisfaction. I have also been informed of whom to contact in case I have more questions. I understand that I have the option of withdrawing at any point in time in the study. I have fully read this consent form and agree to participate in this study".

Name _____Date _____

Study II: Assessing the efficacy of reconsolidation-blockade in EMTs diagnosed with PTSD

Debriefing Form

Thank you for your participation!
In this study, the investigator was interested in assessing the efficacy of reconsolidation-blockade in ameliorating acquired (and subsequently extinguished) fear responses to non-contextual and contextual (EMS-related) stimuli within a fear-conditioning paradigm that used the spontaneous recovery of fear as it's primary measure. Reconsolidation-blockade aims to alter/eradicate the fear memory traces that form upon exposure to traumatic situations by targeting reactivated memories. Previous research has shown that reconsolidation-blockade during extinction training is highly effective in ameliorating acquired fear responses in both human and animal models. The aim of this experiment was to determine if reconsolidation-blockade is just as effective when it comes to 1) contextual, EMS-related stimuli, which is relevant to the emergency response profession and is the primary cause for symptoms of PTSD, and 2) in a cohort that has been repeatedly exposed to multiple potentially traumatic events.

Your participation in this study will help the investigator understand how reconsolidation-blockade can be integrated into the treatment of PTSD for emergency responder. It will also help in understanding how PTSD affects a cohort that is repeatedly exposed to potentially traumatic events.

If you experienced any physical or psychological stress from being in this study, or specifically from being shocked as part of the experiment, please reach out to your squad's chief, established mental health provider or the nearest hospital to receive counseling. You can enter information about your location on this website to determine the nearest medical facility that can assist you: http://www.va.gov/directory/guide/division.asp?dnum=1&isFlash=0

If you have any additional questions or concerns, or would like to know the results of the experiment, please feel free to email Mythili Ananthasayan at ms4487@bard.edu.

If you would like to learn more about fear conditioning, PTSD or reconsolidation-blockade, below are some links to background information and similar experiments that were used as a basis for this study.

http://www.psych.nyu.edu/phelpslab/files/Schiller_nature.pdf- fear-conditioning paradigm and reconsolidation-blockade

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4061428/- reconsolidation-blockade and extinction training

http://www.ptsd.va.gov/professional/PTSD-overview/dsm5_criteria_ptsd.asp- DSM-V criteria for the clinical diagnosis of PTSD

Study II: Assessing the efficacy of reconsolidation-blockade in EMTs diagnosed with PTSD

Timeline

1. Recruitment of participants- 2 months
Use this time to visit various medical emergency response agencies and PTSD treatment centers in New York City to find a clinical sample of EMTs that are diagnosed with PTSD but have not yet started therapeutic/pharmacological treatment.

2. Day 1
Participants will arrive at the lab. They will undergo a structured clinical interview using the CAPS-V to determine presence/severity of PTSD symptoms. They will calibrate the level of shock that feels "highly irritating but not painful" to them. Participants will be hooked up to SCR recording instruments, and the fear-conditioning task will commence, which involves showing each participant 25 presentations of 4 stimuli.

3.Day 2
Participants will come back to the lab and be randomly assigned to one of two groups. The experimental group will be shown 1 presentation of all 4 stimuli in the absence of shocks to reactivate the memory trace from Day 1. Ten minutes after reactivation, both groups will be shown multiple presentations of all four stimuli while being hooked up to SCR recording instruments in the absence of shocks. Stimuli will be shown until the SCR to the CS+ stimuli returns to baseline. The number of extinction trials needed to extinguish the fear response will be recorded.

4.Day 3
Participants will come back to the lab, and will be shown one presentation of all 4 stimuli while being hooked up to SCR recording devices in the absence of shocks.

Study II: Assessing the efficacy of reconsolidation-blockade in EMTs diagnosed with PTSD

Predicted Budget

1. Skin Conductance Measuring System
    - MP150 acquisition system……..≈ $5,300
    - GSR amplifier……≈ $600
    - Electrode gel for GSR electrodes……..≈ $30
    - Transcutaneous Aversive Finger Stimulator……≈ $75
    - Isolated Skin Conductance coupler……..≈ $75
    - Disposable Ag/AgCl electrodes……..≈ $160
    - **TOTAL**……**≈ $6,165**

2. Standard Subject Participation Fees
    - (100 participants * ≈4 hours * $7)……..**≈ $2,800**
3. Assessment Tools
    - Clinician Administered PTSD Scale for DSM-5.....……available to clinicians/graduate students upon requesting the National Center for PTSD

GRAND TOTAL= $6,165 + $2,800 = **$8,965**

Study II: Assessing the efficacy of reconsolidation-blockade in EMTs diagnosed with PTSD

PROCEDURAL DESIGN

DAY 1: Fear conditioning discrimination paradigm (acquisition of fear to CCS+ and NCS+ stimuli)

Presentation of stimuli (100 trials): Stimuli will be presented in random order.

Context-Specific Conditioned Stimulus (CCS+)- 25 presentations, 38% paired with shock

Context-Specific Conditioned Stimulus (CCS-)-25 presentations that are not paired with shocks

Non Context-Specific Conditioned Stimulus (NCS+)- 25 presentations; 38% paired with a shock

Non Context-Specific Conditioned Stimulus (NCS-)-25 presentation that are not paired with shocks

DAY 2: Divide participants into experimental and control groups by random assignment.

- Procedure for experimental group: Reactivation (single presentation of all four stimuli)

All four stimuli (CCS+, CCS-, NCS+ & NCS-) will be presented in the absence of any shocks to reactivate memory of fear acquisition toward CCS+ and NCS+. Participants will wait for 10 minutes after reactivation and will then undergo extinction training. This time period allows for the ameliorative effects of behavioral reconsolidation-blockade to be felt by participants (Schiller et al., 2009).

- Extinction training (repeated presentation of all four stimuli until SCR of participants in response to CCS+ and NCS+ reaches baseline value.




All participants in the experimental group should undergo extinction training, wherein repeated presentations of the CCS+ and NCS+ (which were previously associated with shocks) will render the previous association to fear extinct. Although CCS- and NCS- stimuli were not previously associated with shocks, they will also be presented during extinction training to maintain homogeneity of the experiment.

- Procedure for control group: Extinction training not preceded by reactivation since behavioral reconsolidation blockade depends on reactivation of memory in order to successfully ameliorate or modify fear memory traces.




All participants in the control group should undergo extinction training at the same time and in the same fashion as the experimental group. The main difference between the two groups is the absence of reactivation in the control group's procedure for Day 2.

DAY 3: Final presentation of stimuli and assessment of spontaneous recovery



All participants (regardless of experimental or control group status) will be shown a single presentation of all four stimuli (CCS+, CCS-, NCS+ & NCS-) in the absence of any shocks. SCR will be measured for all four stimuli. Spontaneous recovery will be calculated as (SCR from Day 3- SCR from first trial of extinction on Day 2).