Behavioral interference of Memory Reconsolidation as a Treatment for Post-Traumatic Stress Symptoms

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ABSTRACT

BEHAVIORAL INTERFERENCE OF MEMORY RECONSOLIDATION AS A TREATMENT FOR POST-TRAUMATIC STRESS SYMPTOMS

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Post-traumatic stress disorder (PTSD) is best conceptualized as a failure of the stress response to naturally resolve following trauma exposure (e.g., Orcutt, Bonanno, Hannan, & Miron, 2014). Current treatments are effective for some, but not all who suffer from PTSD (e.g., Bradley, Greene, Russ, Dutra, & Westen, 2005; Lee et al., 2016), and relapse is common (Ursano et al., 2004; Davidson et al., 2001). Considering that PTSD is a memory-based disorder, a treatment that could augment trauma memories has the potential to address the limitations of current interventions. Research on memory suggests that, if a memory is retrieved under the right conditions, it may become temporarily labile and susceptible to interference before it is stored back into long-term memory (LTM) through a process called reconsolidation (e.g., Nader et al., 2000). The reconsolidation literature has led to successful augmentation and erasure of memory using pharmacological intervention in animals and humans (Brunet et al., 2008; Dębiec & LeDoux, 2004), however results are inconsistent (Muravieva & Albirini, 2010; Wood et al., 2015). A behavioral reconsolidation intervention may provide a more flexible approach to memory augmentation. This study attempted to
design and validate such an intervention. Participants \((n = 40)\) were assigned to either the experimental (reconsolidation interference) or the control (traditional exposure) conditions. Psychophysiological arousal, as well as change in overall symptoms, intrusion symptoms specifically, posttraumatic cognitions, and subjective distress, were assessed one week later. Results demonstrated that the intervention paradigm successfully activated participants’ trauma memories, but that it may have failed to initiate reconsolidation processes. No significant differences were found between the experimental and control conditions on any outcome measure. Limitations of this study, future directions, and implications for the behavioral reconsolidation interference paradigm are discussed.
BEHAVIORAL INTERFERENCE OF MEMORY RECONSIDERATION AS A TREATMENT FOR POST-TRAUMATIC STRESS SYMPTOMS

BY
BENJAMIN DARNELL

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A THESIS SUBMITTED TO THE GRADUATE SCHOOL IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE MASTER OF ARTS

DEPARTMENT OF PSYCHOLOGY

Doctoral Director:
David Valentiner
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CHAPTER 1
OVERVIEW

Post-traumatic stress disorder (PTSD) is the only major mental disorder with a clearly recognized environmental cause. PTSD, by definition, results from exposure to a traumatic event. How the disorder develops from the initial trauma and how it is then maintained is not so easily understood. One theory describing how PTSD develops suggests that overactivation of the amygdala suppresses hippocampal consolidation of episodic, or declarative, memory while over-consolidating the emotional content of that memory (Layton & Krikorian, 2002). Until recently, consolidated memory was considered to be permanently fixed. Research, however, has demonstrated that under certain circumstances, the retrieval of a memory causes the memory to become labile (Nader, Schafe, & LeDoux, 2000). A process of reconsolidation must then occur for the memory to once again become stored (Nader et al., 2000). Interference with this reconsolidation process can alter or even eliminate the emotional content of a memory (Nader et al., 2000; Tronson, Wiseman, Olausson, & Taylor, 2006). The ability to change a previously consolidated memory carries important implications for treating memory-relevant mental disorders like PTSD. This study will develop and validate a behavioral protocol for interfering with memory reconsolidation to alleviate post-traumatic stress symptoms (PTSS).

To provide a rationale for this work, first the significance of PTSS, as well as the epidemiology, symptomatology, pathology, and current treatments, will be discussed. Memory encoding, consolidation, and reconsolidation processes will then be outlined. The current
literature on the pharmacological blockade, and then the behavioral intervention, of memory reconsolidation will be presented, then the boundary conditions under which reconsolidation processes may or may not occur will be explained. Finally, the potential for memory reconsolidation interference to be used as a PTSS treatment will be examined and this study described.

Post-Traumatic Stress Symptoms

Significance

Exposure to a traumatic event and the development of symptoms are quite common. Many, if not most, people in the United States will experience a traumatic event in their lifetimes, and this experience will usually result in PTSS development (Kessler, Chiu, Demler, & Walters, 2005; Spoont et al., 2013). Normally, these symptoms subside naturally, however, 8-12% of people will fail to recover (Breslau, Davis, Andreski, & Peterson, 1991; Breslau, Davis, Peterson, & Schultz, 2000; Kilpatrick et al., 2013; Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993; Roberts, Gilman, Breslau, Breslau, & Koenen, 2011). This failure of symptoms to naturally resolve is debilitating and costly. PTSD may lead to significant functional impairment and a low quality of life (Zatzick et al., 1997). Treatment is often difficult and time consuming, and relapse commonly occurs (Davidson et al., 2001; Ursano et al., 2004). For the individual, these treatments may cost thousands of dollars per year (Bass & Golding, 2012). Nationally, disability compensation for PTSD costs billions of dollars annually (Bass & Golding, 2012). Clearly, PTSD is a devastating condition for many reasons, and a treatment that is more effective, less time consuming, and less costly is needed.
PTSD is the experience of certain symptoms as a result of exposure to a traumatic event. A traumatic event can be any event in which a person is exposed to serious harm, such as sexual violence, severe injury, natural disaster, threatened death, or death of another (Giller, 1999). This exposure can be defined as the direct experiencing or witnessing of the event, hearing of a close friend or family member experiencing the event, or repeatedly being exposed to details of the event (American Psychiatric Association [APA], 2013). Considering the wide range of events and varying degrees of exposure that can result in PTSD, there can be a great deal of heterogeneity between the traumatic experiences of people who develop symptoms of the disorder.

The prevalence rate for developing PTSD is relatively low among people who experience traumatic events. Although the rates of experiencing such an event range from 39.1% to 89.7% depending on the population, lifetime prevalence rates of PTSD are only 8.3% to 12.3% (Breslau et al., 1991; Breslau et al., 2000; Kilpatrick et al., 2013; Resnick et al., 1993; Roberts et al., 2011). These statistics indicate that simply being exposed to a traumatic event does not guarantee the development of PTSD. There are many factors that have been found to be associated with an increased risk of PTSD development following trauma exposure. Studies have determined that the strongest predictive factors for the development of the disorder are exposure to severe and violent trauma, previous low self-esteem, being in close proximity to the traumatic event, and having a previous mental health diagnosis (Darvez-Bornoz, et al., 1998; Neria, Nandi, & Galea, 2007). Specific mental health diagnoses that are risk factors for PTSD and that commonly co-occur with the disorder are major depression, anxiety disorders, and substance abuse.
et al., 2006). Other potential risk factors may include being female, having a lower level of education, having less social support, and having a large number of other life stressors present at the time (Brewin, Andrews, & Valentine, 2000).

**Symptomatology**

Considering the heterogeneity of experiences that can result in PTSD, it is not surprising that the disorder can manifest in a wide variety of symptoms. These symptoms are classified by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) into four different clusters (Criterion B-E; APA, 2013) and must be present for at least one month to be considered a PTSD diagnosis (Criterion F; APA, 2013). Criterion B, intrusions symptoms, are symptoms caused by the traumatic memory being activated or re-experienced in some way that is unwanted and distressing. This cluster of symptoms can include dissociation, distressing dreams, involuntary remembering, and psychological or physiological reactions to cues associated with the memory. Criterion C, avoidance symptoms, manifest as an attempt to avoid trauma-related thoughts, memories, emotions, or physical stimuli (e.g., people, places, things). Negative alterations of mood and cognition, Criterion D, includes loss of memory regarding aspects of the traumatic event, overly negative beliefs about yourself or others, self-blame, incessant negative affect, anhedonia, detachment, and inability to experience positive affect. Criterion E includes alterations in a person’s state of arousal, such as irritability, recklessness, hypervigilance, inability to concentrate, problems sleeping, and having an exaggerated startle response (APA, 2013). These criteria can manifest in a variety of combinations and degrees of severity, thus post-traumatic stress symptoms can manifest quite differently from individual to individual.
Although the DSM-5 classifies PTSD as a diagnostic category, research suggests that these symptoms are best viewed as a continuum (Rosen, Spitzer, & McHugh, 2008; Spitzer, First, & Wakefield, 2007). Studies have shown little evidence of PTSD as a natural class, in which people diagnosed with the disorder are qualitatively different than people with similar symptoms that do not meet DSM-5 diagnostic requirements (Broome, 2006; Ruscio, Ruscio, & Keane, 2002). In fact, symptoms are often the same regardless of whether the environmental cause was life stress or a traumatic event (Gold, Marx, Soler-Baillo, & Sloan, 2005), and both PTSD and sub-clinical PTSS lead to similar functional impairments and low quality of life (Bodkin, Pope, Detke, & Hudson, 2007). These similarities suggest that the distinction between trauma and stress is not necessary to understand PTSS (Gold et al., 2005). Furthermore, comorbidities associated with PTSD are the same for sub-clinical PTSS; both populations have high rates of anxiety and depression, and both show an increased risk for generalized anxiety disorder and suicidality (Davidson & Smith, 1990; Jackson et al., 2007; Kazak et al., 2004; Lai, Chang, Connor, Lee, & Davidson, 2004). Treatment is also the same across populations, with the primary focus being the processing of memories surrounding the stressful or traumatic event (Ehlers & Clark, 2000; Foa & Rothbaum, 1998; Pennebaker, 1997). Considering that symptoms, outcomes, comorbidity and treatment are the same for both PTSD and sub-clinical PTSS, and considering that there is little scientific evidence to support PTSD as a category, it may be best to conceptualize PTSS as a continuum of symptoms and not a categorical disorder.

Following a traumatic experience, the development of some PTSS is a normal reaction, although the severity, duration, and response pattern of the symptoms may vary (Morina, Wicherts, Lobbrecht, & Priebe, 2014; Orcutt, Bonanno, Hannan, & Miron, 2014). Once the
initial onset of PTSS has occurred, the natural course of those symptoms may follow one of four prototypical response patterns. The most common response to trauma exposure is called resilience (65% as reported by Orcutt et al., 2014), in which there may be a short period of mild PTSS immediately following the traumatic event, followed by a quick and spontaneous return to pre-trauma levels of functioning (Bonanno & Mancini, 2012; Morina et al., 2014). The second response pattern, gradual recovery (25% as reported by Orcutt et al., 2014), is the initial onset of moderate to severe symptoms that gradually reduce back to pre-trauma levels over the course of months or years following the trauma exposure (Bonanno, 2005). A small number of individuals will experience the third response pattern, called delayed response (<1%, as reported by Orcutt et al., 2014), with mild to moderate symptoms that become more severe over time (Bonanno & Mancini, 2012) or they may develop the fourth pattern, chronic disruption (2% as reported by Orcutt et al., 2014), in which symptoms are severe for an extended period after the initial trauma (Bonanno, 2005). Orcutt et al., (2014) also reported a “moderate impact – moderate symptoms” pattern (8%), in which people with moderate PTSS pre-trauma display high PTSS after the trauma that returns to a moderate level, months later. These many different symptom response patterns and levels of severity that may occur following trauma, coupled with the fact that the onset of some degree of PTSS following trauma is normal, ultimately support the conceptualization of post-traumatic stress reactions as a continuum of symptoms where disorder is characterized by a failure of symptoms to subside.

Pathology.

Information processing models suggest that traumatic events present people with novel information that contradicts information that has been previously stored in long-term memory
(LTM), such as their beliefs about the world (Foa, Steketee, & Rothbaum, 1989; Litz & Keane, 1989; Thrasher, Dalgleish, & Yule, 1994). This dissonance between the new information and the old memory is what produces PTSS as the person tries to process the new information and integrate it with the old. A neurological model described by Layton and Krikorian (2002) outlines the biological processes that may underlie the processing of traumatic information. This model proposes that an over-activation of the amygdala leads to suppression of hippocampal consolidation, resulting in under-consolidation of the declarative content of the memory and over-consolidation of the emotional content. This theory explains why people with PTSS present symptoms even when not having conscious recall of the event. It also explains why they often experience intensified memory for the core traumatic event, but considerably impaired memory for all other events and details surrounding the trauma. Further research has suggested that the medial prefrontal cortex (mPFC), a region of the brain associated with learning, may play a role in PTSS maintenance during reconsolidation of the traumatic memory, whenever the memory is activated. Normal mPFC functioning suppresses amygdalar activity during reconsolidation, allowing the new information to be appropriately integrated with the old memory network (Shin, Rauch, & Pitman, 2006). A failure of the mPFC to down-regulate amygdala activity during reconsolidation leads to an exaggerated emotional response and prolonged dissonance between the old and new information, resulting in chronic PTSS (Shin et al., 2006).

Both information processing and neurological models suggest that it is the failure to appropriately integrate new information into LTM that results in the development of the symptoms outlined in the four symptom clusters of the DSM-5: intrusions, avoidance, negative alterations in mood and cognition, and arousal (APA, 2013). There are many models of the
relationships between the symptom clusters, and many suggestions as to which cluster is at the
core of PTSS (e.g., Brewin, Dalgleish, & Joseph, 1996; Foa, Riggs, & Gershuny, 1995;
Horowitz, 1975). One such model describes each cluster by their relationship to intrusion
symptoms (Creamer, Burgess, & Pattison, 1992; Steil & Ehlers, 2000). In this model, intrusion
symptoms are believed to be central to PTSS as the other symptom clusters can be explained as
ways in which intrusion symptoms are maintained or exacerbated (Creamer et al., 1992; Steil &
Ehlers, 2000). Avoidance symptoms are ways of attempting to deal with distressing intrusions by
trying to push them away or escape (McFarlane, 1992). Research has shown that avoidance often
helps to maintain intrusion symptoms long-term (Creamer et al., 1992; Lawrence, Fauerbach, &
Munster, 1996). It has also been suggested that intrusion symptoms can be exacerbated by the
presence of negative alterations in mood and cognitions. Negative thoughts about intrusion
symptoms (i.e., “having these uncontrollable memories means there is something wrong with
me.”) and distress caused by intrusion symptoms may increase avoidance behaviors, further
maintaining the intrusions (Mayou, Bryant & Duthie, 1993; Rachman & de Silva, 1978, Steil &
Ehlers, 2000) Arousal symptoms may increase the severity of all other symptom clusters, which
further exacerbates this process of intrusion maintenance (Schell, Marshall, & Jaycox, 2004; Tull
& Roemer, 2003). Considering that many of the symptom clusters are the result of intrusions
and all clusters work to maintain intrusions, intrusion symptoms can be considered the core
symptom cluster of PTSS.

Treatment

There are many treatments available for PTSS. Several prescription drugs, such as
selective serotonin reuptake inhibitors, have been shown to be effective pharmacotherapies
(Stein, Ipser, & Seedat, 2006). These drugs work by modulating the levels of neurotransmitters that are believed to play a role in acute stress (Stein et al., 2006). Although these drugs have been shown to be better at symptom control than placebos, they merely suppress symptom levels and do not lead to real, lasting change (Lee et al., 2016; Otto, Penava, Pollack, & Smoller, 1996; Van Etten & Taylor, 1998). In contrast, psychotherapies have been shown to be equally if not more effective at treating PTSS across all outcome domains (e.g., symptom reduction and patient attrition), while also having long-term efficacy of treatment (Lee et al., 2016; Otto et al., 1996; Van Etten & Taylor, 1998).

Psychotherapies have been shown to result in 40%-70% of clients seeing significant reduction in their symptoms, as determined by a meta-analysis of 26 studies (Bradley, Greene, Russ, Dutra, & Westen, 2005). This analysis compared exposure-based, cognitive-behavioral, combined exposure and cognitive-behavioral, eye movement desensitization and reprocessing, and other therapies. The total number of participants across all 26 studies was 1,535 and the mean length of treatment was 15.64 hours ($SD = 10.52$). The overall effect size was large for studies that compared PTSD symptoms pre-treatment to post-treatment ($d = 1.43$), as were the effect sizes when comparing the treatment condition to a wait-list control ($d = 1.11$) or to a control given non-therapeutic support ($d = 0.83$). This pattern of results suggests that psychotherapies are a fairly effective way of treating PTSD. Comparing each therapy to all other therapies included in the study found no major differences in outcome. For all studies combined in the meta-analysis, 56% of participants who entered treatment and 67% of those who completed treatment no longer met DSM criteria for PTSD. Although this meta-analytic finding is impressive considering that PTSD is often a chronic disorder, a large portion of the treatment
population of each individual study (30%-60%) did not show significant improvement. This meta-analysis did not look at how long any improvement may have lasted in successfully treated individuals.

**Therapy as Extinction.**

Exposure-based therapies, specifically Prolonged Exposure Therapy, are some of the most empirically supported treatments for PTSS (Foa, Keane, Friedman, & Cohen, 2009; Foa, Rothbaum, Riggs, & Murdock, 1991; Taylor et al., 2003). Generally speaking, the use of exposure therapy is based on the idea that PTSS develops through classical conditioning (McLean & Foa, 2011). In classical conditioning, an unconditioned stimulus (US) provokes an unconditioned response (UR), then is repeatedly paired with another stimulus that is not inherently tied to the UR. Eventually, an association is formed between this second stimulus, called the conditioned stimulus (CS) and the US. This association then leads to an association between the CS and the UR, which continues as a conditioned response (CR) even after the removal of the US.

In the case of PTSS, the US is the traumatic event and the UR is the fear of a negative outcome, such as death or injury (McLean & Foa, 2011). The fear response (the UR) quickly becomes associated with a number of nonthreatening cues (the CS) during the traumatic event, which now trigger the fear (the CR). Exposure therapy then works by engaging extinction learning, in which the CS is presented repeatedly without the CR so that new learning takes place that does not associate the CS with the CR. For PTSS, the non-threatening cues are confronted repeatedly with no negative outcome (McLean & Foa, 2011). This confrontation can be done
either imaginally, in which the memories of the traumatic event are recalled in vivid detail, or in vivo. The repeated exposure to these cues (CSs) with no negative outcome (CR) results in the learning that the cues are not associated with the negative outcome, and the fear response diminishes (McLean & Foa, 2011).

Memory Processes

Encoding

Memory encoding is the process of translating raw sensory input data into meaningful information that can be stored in long-term memory (LTM). During any experience, the activation of sensory receptors triggers activation of sensory regions of the brain (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). These regions refine the sensory signals and send them to the appropriate areas for further refinement into a single signal for storage. The areas that ultimately encode the sensory signals into information for storage differ depending on the type of memory that will be created. Implicit memory is the nonconscious memory of procedural tasks and skills, such as how to ride a bike or write your name. These memories are encoded by the areas of the brain involved in motor control, such as the cerebellum, caudate nucleus, and motor cortex (Reber, 2013). Explicit memories can be consciously retrieved and are the memories of events and facts that have been learned. Many regions of the brain may be involved in the encoding of explicit memory, with some of the best studied regions within the medial temporal lobe (MTL; Reber, 2013). The role of the MTL in explicit memory encoding was famously demonstrated by Scoville and Milner (1957) when they removed a large portion of the MTL from patient HM to relieve his epilepsy. After the surgery, HM lost the ability to form
new explicit memories, yet was still able to form new implicit memories. This case study demonstrates the differential localization of explicit and implicit memory encoding and highlights the importance of MTL regions for explicit memory formation.

**Consolidation**

Research since patient HM has demonstrated that MTL regions, specifically the hippocampus, are involved in not just the encoding of explicit memories, but also the consolidation of these memories (Bayley, Hopkins, & Squire, 2003; McClelland, McNaughton, & O’Reilly, 1995; O’Reilly, Bhattacharyya, Howard, & Ketz, 2011; Squire & Alvarez, 1995; Squire, Clark, & Knowlton, 2001). Memory consolidation is the process following encoding in which the new memory is stabilized and stored into LTM (Nadel & Moscovitch, 1997). This process has been proposed to occur on two levels: through synaptic consolidation, which occurs within hours of memory encoding, and through systems consolidation, which may take days or even years to complete (Dudai, 2004). Synaptic consolidation requires the creation and strengthening of neuronal synapses. For explicit memory, sensory input leads to activation of neurons throughout the cortex and within the hippocampus. The simultaneous firing of the cortex neurons may cause the formation of new synaptic connections between these neurons (Bliss & Gardner-Medwin, 1973; Bliss & Lømo, 1973; Doyere & Laroche, 1992; Hebb, 1949; Konorski, 1948; Morris, Davis, & Butcher, 1990). These new connections are temporary and may only become stronger and more permanent through continued activation (Kelso, Ganong, & Brown, 1986; Malinow, 1991; Malinow & Miller, 1986; Sastry, Goh, &Auyeung, 1986). The phenomenon of neurons creating stronger and longer-lasting synaptic connections by repeatedly
firing simultaneously is called long-term potentiation (LTP; Bliss & Collingridge, 1993). LTP of the cortex neurons may occur due to the activation of the hippocampal neurons. Explicit memory encoding may trigger rapid synaptic formation and activation between hippocampal neurons. It has been theorized that, when stimulation of the neurons ends, they perseverate and remain active in what is called a reverberating memory trace (Gerard, 1949; Hebb, 1949; McGaugh, 1999). The reverberating trace in the hippocampus has been theorized to maintain the memory while facilitating the LTP of the neurons in the cortex (Hebb, 1949; Martinez & Derrik, 1996). The LTP of the neurons in the cortex may strengthen the connections between those neurons, creating permanent structural changes in the cortex, while the reverberating trace in the hippocampus degrades as it becomes less necessary to maintain the memory. It has been proposed that this transfer of activity from the hippocampus to cortical areas may lead to systems consolidation, where structural changes in the brain allow the new memories to become independent of the hippocampus (Bontempi, Laurent-Demir, Destarde, Jaffard, 1999: Dudai, 2004; Haist, Gore, & Mao, 2001; Wang, Hu, & Tsien, 2006).

Evidence suggests the presence of emotion during an event as a strong factor that moderates consolidation of an explicit memory (Christianson, 2014). The emotional content of a memory may undergo the memory encoding and consolidation processes in the amygdala (Pelletier, Likhtik, Filali, & Paré, 2005). It has been proposed that emotional arousal during an event may shift attention to the source of the arousal and increase alertness, altering the perspective of the event and determining what information gets encoded (Hamann, 2009). This arousal may coincide with amygdala activation, which may enhance encoding of the episodic content of the explicit memory by upregulating hippocampal activity (Hamann, Ely, Grafton, &
During consolidation of the explicit memory, structural changes in the lateral and basal amygdala may result in long-term storage of the emotional content of the memory (Hamann, 2009; Pelletier et al., 2005). The stored emotional content may be connected to other parts of the memory during the consolidation process, moderating the strength and subjective quality of the stored memory (Hamann, 2009; Liang & McGaugh, 1983; Pelletier et al., 2005; Roozendaal & McGaugh, 1996).

The structural changes produced by LTP occurring during consolidation in both the hippocampus and the amygdala may be dependent on a protein synthesis cascade (Nader et al., 2000). This theory suggests that the reverberating memory trace creates an increased rate of depolarization in postsynaptic neurons (Wang et al., 2006). This depolarization may trigger the voltage-gated N-methyl-D-aspartate receptor (NMDAR), to increase calcium ion flow into the cell (Bliss & Collingridge, 1993; Tsien, Tonegawa, & Huerta, 1997). The influx of calcium may activate enzymes that trigger mitogen activated protein kinase (MPAK), which turns on extracellular signal regulated kinase (ERK) through phosphorylation (Tronson & Taylor, 2007). ERK phosphorylates transcription factors such as cyclic AMP-response element binding protein (CREB) and ELK1, which bind to DNA and initiate mRNA transcription. This process may be aided by activation of α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), which aid in the depolarization of the NMDAR membranes. AMPARs also may increase cyclic adenosine monophosphate (cAMP) which triggers cAMP-dependent protein kinase (PKA), which may directly activate transcription factors or indirectly activate them by phosphorylating ERK and ribosomal protein S6 kinase. The transcribed mRNA upregulates AMPAR, which are important in glucose-dependent intercellular communication. Protein
synthesis may also increase the dendritic spine density of the neuron, and produce brain-derived neurotrophic factor (BDNF), which is involved in neurogenesis (Rossi, et al., 2006; Scharfman, et al., 2005). The upregulating of AMPARS and dendritic spine density may increase the postsynaptic neuron's sensitivity to the presynaptic neuron’s signaling, while neurogenesis creates new cells that may wire into the memory formation (Tronson & Taylor, 2007). The result of this process may be a stabilized neural network that contains a fully consolidated memory (Tronson & Taylor, 2007).

**Reconsolidation**

For decades, the idea that once memories were consolidated, they were permanently stable and fixed in the brain was the most widely held view of memory processes (Nader, 2013). Recent developments in research have strongly suggested that whenever a memory is retrieved, it becomes labile and requires a process of reconsolidation to be stored in LTM again. This process was first demonstrated by Misanin, Miller, & Lewis (1968) using electroconvulsive therapy to block the reconsolidation process, however, reconsolidation did not receive mainstream scientific recognition or support until the publication of a 2000 study by Nader, Schafe, and LeDoux. In this study, mice that had been trained to fear a stimulus were given a single exposure to that stimulus one day later in order to activate the fear memory. After activation, the mice received an injection of the protein synthesis inhibiting drug anisomycin directly into the amygdala. Results showed significant impairment to the consolidated fear memory only when the mice had received that single memory activating exposure and only then if the anisomycin injections occurred within six hours of retrieval. This study was the first to show that memories require a
protein dependent reconsolidation process, similar to the initial consolidation process, and that blocking the protein synthesis cascade during reconsolidation impairs a previously consolidated memory (Nader et al., 2000).

The process of reconsolidation involves the same areas of the brain as consolidation, such as the hippocampus and the amygdala (Dębiec, LeDoux, & Nader, 2002; Schafe & LeDoux, 2000). However, unlike consolidation, reconsolidation first requires the destabilization of a memory (Alberini & LeDoux, 2013). It has been suggested that this destabilization is dependent on the degradation of proteins, as well as the activation of glutamate receptors, NMDARs, and cannabinoid receptors (Alberini & LeDoux, 2013; Monfils, Cowansage, Klann, & LeDoux, 2009). The reconsolidation of the newly updated memory after destabilization may then require a similar protein syntheses cascade as the one required in consolidation, with the activation of NMDARs resulting in morphological synaptic changes and cellular growth (Tronson & Taylor, 2007).

It is likely that the memory reconsolidation process evolved as a way to efficiently update memories when presented with new and relevant information (Alberini, 2005; Alberini & LeDoux, 2013). An organism with memories that can be updated whenever they are retrieved has the advantage of being able to learn and form strong memories about danger and rewards without having to re-experience the exact same scenario multiple times (Alberini & LeDoux, 2013). All that is required to update a previously learned memory is a similar or related event to trigger the initial memory, and new information can be integrated and stored. This updating process allows for an adaptively speedy mechanism for learning in a changing environment (Alberini & LeDoux, 2013).
Pharmacological Blockade of Memory Reconsolidation

Animal Models

Further research has supported memory reconsolidation as a unique process through selective pharmacological blockade of the protein syntheses cascade. Although the protein cascade required for reconsolidation is similar to consolidation, animal models have demonstrated a few key differences. These differences are the activation of the transcription factor zinc finger 268 instead of BDNF as in consolidation, as well as the reversal of the role of CCAAT-enhancing binding protein-β, which is used exclusively in the amygdala during reconsolidation but is specific to the hippocampus during consolidation (Alberini, 2005; Tronson & Taylor, 2007). These differences show that reconsolidation is not only a different process from extinction, but that it is distinct from consolidation as well.

Animal models of reconsolidation interference have also been successful in blocking reconsolidation of fear memory using pharmacological techniques. When administered immediately prior or immediately post memory reactivation, kinase activity inhibitors, protein synthesis inhibitors, and β-adrenergic or glucocorticoid antagonists have all been shown to be successful at altering or preventing reconsolidation of the fear memory. A PKA inhibitor administered directly to the basolateral nuclei of the amygdala resulted in significantly decreased fear response in rats both one and seven days post-injection (Tronson et al., 2006). Similarly, injections of the protein synthesis inhibitors cycloheximide and anisomycin both successfully prevented the return of fear in tests of spontaneous recovery, renewal, and reinstatement 23 days after administration (Duvarci & Nader, 2004; Duvarci, Nader, & LeDoux, 2005). Despite these encouraging findings, translating these results into clinical use is impractical, as many effective
pharmacological agents are either toxic to humans or they require direct injection into the brain (Monfils et al., 2009). Protein synthesis inhibitors have also been shown to be significantly less effective when used to block reconsolidation in older memories (Milekic & Alberini, 2002).

Two promising drugs that overcome many of these problems are the β-adrenergic antagonist propranolol and the glucocorticoid antagonist mifepristone. Propranolol has been used to successfully block fear memory reconsolidation in rats, with decreases in fear response being maintained for at least one month (Dębiec & LeDoux, 2004; Przybyslawski, Roullet, & Sara, 1999). Mifepristone has shown similar ability to block the return of fear in rats 12 days after administration, although these effects were not seen when administered concurrently with propranolol (Pitman et al., 2011). Both drugs are non-toxic to humans and do not require direct-injection, making them ideal candidates for the study of reconsolidation interference in humans.

Although propranolol has received considerable attention as a potential agent to target memory reconsolidation processes in humans, one study by Muravieva and Albirini (2010) casts doubt on the efficacy of the drug for all types of fear memories. In this study, the effects of propranolol administration on cued and contextual fear conditioning memories were compared to its effects on a memory of inhibitory avoidance. For the cued and contextual memory, rats were trained to fear a sound in one context, were re-exposed to that sound in a different context, and then received an intraperitoneal (i.p.) injection of propranolol. Forty-eight hours later, the rats were placed into the first context to test for contextual fear memory response. Two days following, they were re-exposed to the sound in the second context to assess for cued fear memory response. In both cases, no significant difference was found between naïve rats and rats injected with propranolol.
To test disruption of an inhibitory avoidance memory, rats received a foot shock whenever they entered a dark room in order to train them to avoid that room. Forty-eight hours later, the rats were placed in the dark room and shocked again to activate the memory, receiving i.p. injections of propranolol either immediately before or after testing. Another forty-eight hours later, all rats were tested again but allowed to avoid the room, in order to assess for inhibitory avoidance. Results showed that the rats who were injected before test one showed no avoidance during test one, but did show avoidance in test two. Rats injected after test one showed avoidance during both tests.

These studies indicate that propranolol blocks reconsolidation of cued and contextual fear conditioning, but does not block the reconsolidation of inhibitory avoidance memories. It may, however, impair retrieval of inhibitory avoidance memories if administered before memory activation. These findings suggest that propranolol has limited efficacy when administered for memories involving avoidance. Considering that real traumatic memories often involve avoidance, are more complicated, and are often older and stronger than the fear learning memories that are studied in the lab, this study suggests that pharmacological interventions are not capable of addressing all of the factors that are involved in actual traumatic memories.

**Human Models**

**Brunet et al. (2008)**

A study by Brunet et al. (2008) examined the effects of propranolol on memory reconsolidation in individuals with PTSD. Nineteen participants wrote in detail about the traumatic event that caused their PTSD symptoms. This writing involved the preparation of two
scripts per subject, with each script targeting a different aspect of their traumatic event. When the writing was complete, the researcher read each script and requested more information when necessary. This script preparation procedure reactivated the trauma memory, after which participants received either 40 mg short-acting propranolol or a placebo.

After a week had passed, participants returned to the lab for the follow-up procedure. Baseline heart rate (HR), skin conductance (SC), and electromyogram (EMG) responses were recorded for 30-seconds. After baseline data was collected, participants listened to 30-second recordings of each of their two scripts. These scripts were composed and pre-recorded by the researcher. After listening to these scripts, the participant was asked to imagine the traumatic event for 30-seconds. Responses for HR, SC, and EMG were calculated by subtracting the mean follow-up baseline score from the mean imaginal exposure score. A multivariate analysis of variance (MANOVA) was used to analyses the psychophysiological data, with HR, SC and EMG as dependent variables. Psychophysiological responses were also subjected to independent t-tests.

Analysis found HR and SC of participants to be significantly lower in the propranolol condition compared to the placebo control. HR and SC were also found to be below the typical PTSD cutoff for the propranolol condition and not for the control, although only HR was significantly lower. EMG was not found to be significantly different between conditions, and both the propranolol and the placebo conditions showed EMG responses below the typical PTSD cutoff. The effect sizes (Cohen’s d) were found to be very large for SC (d=1.23), large for HR (d=0.92), and small for EMG (d=0.29). Despite the poor EMG results, the findings from this
study using HR and SC support the effectiveness of propranolol to block reconsolidation in human subjects.

Wood et al. (2015)

Three studies by Wood et al. (2015) examined the reconsolidation interference capabilities of propranolol, mifepristone, and combined mifepristone and D-cycloserine, a NMDA partial agonist that may enhance learning and extinction (Monahan, Handelmann, Hood, & Cordi, 1989; Richardson, Ledgerwood, & Cranney, 2004). In all three studies, participants with PTSD were asked to describe their traumatic event in order to retrieve the memory and drugs were administered. One week following the activation trial, participants returned and engaged in script-driven traumatic mental imagery while HR, skin conductance, and facial electromyogram responses were recorded. None of their three studies found any physiological differences between control and experimental conditions, nor were any decreases in PTSS observed. This study contradicts the findings of Brunet et al. (2008) suggesting that pharmacological interventions may have difficulty targeting memory reconsolidation processes in humans. The activation and completion of memory reconsolidation only occurs under certain boundary conditions, and it is likely that these contradictory findings are due to Wood et al. (2015) inadvertently violating one of these boundaries. For example, research has suggested that reconsolidation processes are only activated when novel or contradictory information is presented during activation (Díaz-Mataix, Martinez, Schafe, LeDoux, & Doyère, 2013; Sevenster, Beckers, & Kindt, 2013, 2014; Winters, Tucci, & DaCosta-Furtado, 2009) and when the activation cue is neither too short or too long, with the duration of the cue being determined
by the age and the salience of the memory (Bustos, Maldonado, & Molina, 2009; Frankland et al., 2006; Lee, Milton, & Everitt, 2006; Robinson & Franklin, 2010). It is possible that the Brunet et al. (2008) study used more accurate cue durations for their sample than Wood et al. (2015), or that they inadvertently introduced sufficient novel information where Wood et al. (2015) did not. Unfortunately, pharmacological interventions are rigid in their administration and cannot be easily tailored to the complexities of traumatic memories and the boundaries that govern memory reconsolidation. Considering the limited support between Brunet et al., (2008) and Wood et al. (2015) for the efficacy of drugs for human reconsolidation interference, as well as the evidence from animal models that pharmacological blockade of reconsolidation may not be possible with avoidance relevant memories, a behavioral intervention to target reconsolidation processes may provide a more flexible and reliable method for human reconsolidation interference.

Behavioral Interference of Reconsolidation

Erasure vs. Extinction.

In studies looking at non-pharmacological methods of reconsolidation interference, most paradigms compare memory erasure to extinction. Reconsolidation interference and extinction differ procedurally, biologically, and cognitively, as well as in the outcomes they produce. Reconsolidation is activated by a short memory re-exposure, but a long re-exposure triggers extinction (Kim & Fanselow, 1992; Maldonado, 2003; Pedreira & Eisenburg, Kobilo, Berman, & Dudai., 2003; Suzuki et al., 2004). This difference has been demonstrated by using protein synthesis inhibitors to target fear memories in mice after both short and long memory re-
exposures (Suzuki et al., 2004). After short re-exposure, the memory is attenuated as the inhibition of the protein synthesis cascade results in interference with the memory reconsolidation process. After the long re-exposure, the memory remains unaffected, as protein inhibition blocks the consolidation of the new extinction memory (Suzuki et al., 2004). These different re-exposure lengths activate different anatomical regions of the brain to initiate their respective processes. Extinction of fear memories seems to occur primarily in the amygdala and mPFC, and reconsolidation processes occur in the amygdala and hippocampus (Burgos-Robles, Vidal-Gonzalez, Santini, & Quirk, 2007; Dębiec et al., 2002; Mamiya et al., 2009; Santini, Ge, Ren, de Ortiz, & Quirk, 2004).

On the cognitive level, these two processes differ in their relationship to the original fear memory. Extinction does not result in the weakening of the stimulus-response association, as evidenced by the return of fear phenomena. These phenomena are ways in which the fear association may be detected after successful extinction. Reinstatement occurs when exposure to the US leads to the return of fear when the CS is later presented. Context renewal is when exposure to a new environment following extinction results in the return of fear. Reacquisition is when fear learning occurs significantly faster for a subject with an extinguished fear than for a naïve subject. Spontaneous recovery is when the fear association returns unprovoked, as a function of time. The existence of these phenomena suggest that extinction does not lead to the weakening or elimination of a learned fear. Instead extinction results in the development of a new memory that competes with the fear association (Alberini, 2013). At first, this new memory is able to suppress the effects of the fear memory, however, over time or under certain conditions the fear memory can override the extinction memory and result in the return of fear.
Demonstration of memory erasure requires the absence of any of the return of fear phenomena; a subject with an erased memory should appear no different than a naive subject. Since memory reconsolidation interference does not create a new memory but instead disrupts the original memory, it is able to permanently weaken or erase fear associations (Alberini, 2013). In a paradigm looking at memory erasure versus extinction in a population with PTSS, intrusion symptoms could be used as a proxy for return of fear. Intrusions are necessarily memory dependent, as they often involve the unwanted re-experiencing of the traumatic event (Hackmann, Ehlers, Speckens, Clark, 2004; Steil & Ehlers, 2000). In this paradigm, the recovery from and eventual return of intrusions may therefore be considered a marker of extinction, where the permanent elimination of these symptoms would mark reconsolidation interference.

**Animal Models**

A paradigm to erase fear memories during the reconsolidation window has been successfully developed using animal models. This paradigm was developed and tested by Monfils et al. (2009) in a series of six experiments. In the first experiment, the effect of this paradigm on spontaneous recovery was examined. Rats were conditioned to fear a stimulus, then 24 hours later that fear memory was activated. After activation, extinction trials were administered either during the reconsolidation window (10 minutes or one hour after activation) or outside the window (six or 24 hours). One month following activation, rats that received extinction training outside the reconsolidation window, but not the rats that received training inside the window, showed spontaneous recovery of fear as measured by freezing response (Monfils et al., 2009).
The second and third experiments assessed the behavioral paradigm’s effect on context renewal and reinstatement of fear, respectively (Monfils et al., 2009). In the renewal experiment, rats were conditioned to fear a stimulus in context A, then 24-hours later either received an activation trial in context B followed by extinction, or just received extinction. One day later, the rats were tested for the return of fear in context B, then 24-hours following were tested again in context A. This study found that rats that did not receive the activation trial showed renewal of fear in the context in which the fear memory was first formed. Rats that did receive the activation trial did not show fear renewal. In the reinstatement experiment, rats were trained to fear a stimulus by pairing it with a foot shock, then received a series of unpaired shocks 24-hours after memory activation and extinction. The next day, testing for reinstatement of fear revealed that only the mice that received the activation trial did not experience reinstatement (Monfils et al., 2009).

Two other experiments by Monfils et al. (2009) demonstrate that behavioral interference of memory reconsolidation leads to decreased re-acquisition of fear by showing that rats have significantly more difficulty being re-conditioned to fear a stimulus after completing the behavioral intervention paradigm. These studies used a single pairing and five pairings to recondition the animals, respectively. The final of the six studies demonstrated the differing molecular mechanisms between behavioral interference of memory reconsolidation interference and extinction. All six of these studies together demonstrate the ability of a behavioral intervention to target distinct reconsolidation processes to permanently erase fear (Monfils et al., 2009). Although these studies are the only ones to design and test such a paradigm using an animal model, attempts to translate these methods to human use have been successful.
Human Models

Schiller et al. (2010)

Although behavioral intervention of memory reconsolidation for existing fear memories has yet to be reported at the time of this writing, the behavioral paradigm used in laboratory-conditioned animal models has been successfully translated to human use by Schiller et al. (2010) for laboratory-conditioned fear. Participants in this study underwent fear conditioning to an electric shock, then one day later, were given extinction training either with or without prior memory retrieval. Those that were in the memory retrieval condition were further divided into a condition that received training 10 minutes after retrieval and a condition that received training 6 hours after retrieval. Spontaneous recovery was assessed 24 hours later by measuring participant SC response when presented with the CS without the US. Reinstatement was assessed both one day and one year later by measuring participant SC response when presented with only the CS after experiencing four unsignaled shocks in the original experiment room. All three conditions showed a significant increase in fear response as measured by SC after conditioning followed by a return to non-significant levels of fear following extinction. Both one day and one year after testing, the return of fear was found in the no retrieval and the retrieval-6-hour conditions, but not the retrieval-10-minute condition, consistent with extinction conducted within a specific time window after memory retrieval permanently eliminating the fear memory.

Oyarzún et al. (2012).

The findings of Schiller et al. (2010) were replicated by Oyarzún et al. (2012) using a within-subjects design and auditory aversive stimuli. In this study, all participants underwent
conditioning with three differently colored squares as stimuli. Two of these squares were paired with two different aversive sounds, resulting in the conditioned fear of these squares. The third square was used as a neutral stimulus with no sound pairing. One day after conditioning, a single presentation of the neutral stimulus was administered, along with a single presentation of one of the fear-conditioned stimuli in order to activate the learned fear memory for that stimulus (Stimulus A). The other fear-conditioned stimulus was not used in a memory activation trial (Stimulus B). Immediately following the memory activation trial for Stimulus A, fear extinction trials were conducted for both Stimulus A and B, and a similar trial was conducted with the neutral stimulus. The following day, spontaneous recovery and reinstatement of fear were tested for both fear conditioned stimuli. Both spontaneous recovery and reinstatement were significantly decreased for Stimulus A compared to Stimulus B, as measured by SC. There were no significant differences in spontaneous recovery or reinstatement between Stimulus A and the neutral stimulus. These findings show a return of fear only with the fear-conditioned stimulus that did not receive an activation trial prior to extinction (Stimulus B). In contrast, the fear-conditioned stimulus that did receive the activation trial (Stimulus A) elicited the same amount of fear response as a non-feared stimulus (the neutral stimulus). These results suggest that this behavioral paradigm successfully erases fear memory, so that a fear-relevant stimulus becomes no different than a neutral stimulus and both are significantly different from a fear-relevant stimulus that was simply extinguished. Because this study was able to replicate the findings of Schiller et al. (2010) using a novel feared stimulus (aversive auditory stimuli vs. electric shock), this study supports the use of this behavioral paradigm for reconsolidation interference for a variety of stimuli.
The Schiller et al. (2010) study was further replicated by Björkstrand et al. (2015). Participants in this study were trained to fear a visual stimulus by pairing that stimulus with an electric shock. The next day, participants received a two-minute memory activation trial, then received extinction training either 10 minutes or six hours later. One day later, renewal of fear was tested with fMRI scans of the basolateral amygdala. Participants that had received extinction training 10 minutes following memory activation demonstrated less basolateral amygdala activity compared to those who received extinction outside the reconsolidation window (six hours after activation). The amygdalar activation of the later condition predicted fear reacquisition in participants tested 18-months after fear conditioning, as measured by SC. The results of this study show that the return of a learned fear association at three-days and 18-months post-conditioning was present in only the condition (the six-hour condition) that received extinction training outside the reconsolidation window. These findings also successfully demonstrate the ability of a behavioral paradigm to permanently erase laboratory-conditioned fear memories in humans.

Ecological Validity.

Reconsolidation models state that reconsolidation processes exist as adaptive measures for the expedient updating of old memories with new, relevant information (Alberini & LeDoux, 2013). These processes are adaptive because the organism does not have to experience the same
event multiple times to learn new information. Instead, it can experience a similar event that triggers the old memory, and that memory can then be altered to incorporate this new information (Alberini & LeDoux, 2013). Based on this idea, reconsolidation models predict that fear relevant memories of one event would be attenuated after exposure to a similar, but less fear inducing second event. The study by Weems et al. (2014) demonstrated the ecological validity of memory reconsolidation models by testing this prediction in a natural setting.

In this study, students in two separate samples that experienced Hurricane Katrina were asked to write down an account of the event. Later, following exposure to a second storm (Hurricane Gustav), the students were again asked to write down their account of Katrina. A significant decrease in negative memories of Katrina was predicted by low negative Gustav exposure in both samples. It was theorized that exposure to Gustav initiated recall of the memories of Katrina, and for those participants that did not have a highly negative experience with Gustav, the new safety information was incorporated into the old Katrina memory. This change in the original Katrina memory does not reflect the mere learning of new safety information, as the memories of Katrina themselves were altered to be less negative. Instead the attenuation of the original memory suggests that memory reconsolidation processes changed that memory to match the new information presented by Gustav. The demonstration by Weems et al. (2014) that long-term memories can be updated without pharmacological intervention lends ecological validity to the memory reconsolidation models. When new information was presented that was relevant to the memory of Hurricane Katrina, this information was naturally incorporated into the original memory, thus allowing participants to quickly adapt to the new safety information.
The ecological validity of memory reconsolidation models has also been demonstrated in a population exposed to the Boston City Bombing (Kredlow & Otto, 2015). In this study, 113 undergraduates with varying degrees of exposure to the Boston City Bombing were asked to answer questions about the bombing and describe it in as much detail as possible, as a way of activating the memory (Time 1). Participants were then given either no interference task or were asked to read a negative, positive, or neutral story. After one week, the participants were given the same retrieval task as at Time 1. A significant decrease in memory details was found, but only in the condition that received the negative story interference task. Memory reconsolidation models state that interference during the reconsolidation process will impair a previously consolidated memory. The findings of Kredlow and Otto (2015) support the ecological validity of these models by showing that an interference task after activation of a real traumatic memory results in a decrease in the declarative content of that memory. It is important to note that the emotional valence of the interference task determined whether reconsolidation interference was successful. It is possible that interference task valence represents a boundary condition for the interference of reconsolidation for declarative content in memories. Although this finding has not been demonstrated in studies testing reconsolidation interference of emotional content, other studies have supported the existence of boundary conditions under which a memory may become more or less susceptible for erasure (Björkstrand et al., 2015; Bustos et al., 2009; Deębiec et al., 2006; Díaz-Mataix et al., 2013; Forcato, Argibay, Pedreira, & Maldonado, 2009; Frankland et al., 2006; Lee et al., 2006; Lee, 2010; Monfils et al., 2009; Nader et al., 2000; Oyarzún et al.,
A study by Soeter and Kindt (2011) looked at both pharmacological and behavioral intervention of memory reconsolidation in humans. In this study, participants underwent fear learning to two fear-relevant stimuli for both the drug and the behavioral paradigms. On the second day for the drug paradigm, participants received either a single dose of propranolol or a placebo immediately prior to memory activation of one of the stimuli. For the behavioral paradigm, participants engaged in activation to one of the stimuli, then waited 10 minutes before extinction trails were administered for both stimuli. On the third day, participants in the experimental conditions for both the drug and behavioral paradigms showed no spontaneous recovery as measured by fear-potentiated startle response (FPS), compared to the control stimulus. Participants in the pharmacological but not the behavioral paradigm showed no reacquisition of fear, as measured by FPS. No difference was found for SC and subjective units of distress (SUDS) between the experimental and control stimuli for either paradigm.

This study partially conflicts with the findings of previous studies (e.g., Brunet et al., 2008; Schiller et al., 2010), as differential SC activation between experimental and control stimuli was not demonstrated. This discrepancy is particularly troubling, as SC is the most common method of measuring fear response in studies of memory reconsolidation interference (e.g., Björkstrand et al., 2015; Brunet et al., 2008; Oyarzún et al., 2012; Schiller et al., 2010; Wood et al., 2015). Another problematic finding was the limited efficacy of the behavioral
paradigm. Although both propranolol and post-reactivation extinction trials led to decreased spontaneous recovery, only participants in the behavioral paradigm showed fear reacquisition. These problematic findings might be explained by differences between this study and other, more successful research. Most importantly, other studies have shown that activation cues need to be longer for stronger memories (Frankland et al., 2006; Robinson & Franklin, 2010). Soeter and Kindt (2010) utilized similar length activation cues as used in previous studies, despite their stimuli being more fear-relevant (i.e., pictures of a spider and a gun) compared to the fear-conditioning stimuli in other research (i.e., colored shapes). It is possible that these fear-relevant stimuli are more strongly consolidated in memory, and therefore require a longer activation cue. It is also possible that, due to the increased fear-relevancy of the stimuli, participants continued to think about the stimuli during the 10-minute break between activation and extinction, in the experimental condition. Failing to cognitively disengage with the stimuli would mean that no real break occurred between the activation trial and extinction, effectively turning the activation trial into the first extinction trial and engaging extinction mechanisms instead of reconsolidation processes (Bustos et al., 2009; Lee et al., 2006). In order to ensure that reconsolidation is activated over extinction, participants would need to be distracted from the fear-relevant stimuli during the break between activation and extinction. These two limitations of the Soeter and Kindt (2010) study represent two important boundaries that determine whether a memory is successfully destabilized and whether memory reconsolidation interference is possible. These and other boundaries of reconsolidation have been suggested by the reconsolidation literature. Any study seeking to interfere with memory reconsolidation processes would need to take these boundaries into account in order to successfully activate and attenuate a memory.
Boundaries of Reconsolidation

Fear memory attenuation using the extinction paradigm has been demonstrated in studies showing both short and long-term persistence with psychophysiological and fMRI measures (Björkstrand et al., 2015; Oyarzún et al., 2012). However, similar findings have not been found in every case (Soeter & Kindt, 2011), leading researchers to examine the boundary conditions under which reconsolidation takes place. The most studied of the parameters of reconsolidation is the period of time after memory retrieval. Animal and human studies both indicate that reconsolidation lasts no longer than six hours after the memory is activated (Björkstrand et al., 2015; Monfils et al., 2009; Nader et al., 2000; Schiller et al., 2010). Any attempts at interference before memory activation or after this window is not believed to engage the reconsolidation process and will not result in persistent changes to memory (Björkstrand et al., 2015; Monfils et al., 2009; Nader et al., 2000; Schiller et al., 2010).

The cue that activates the memory cannot last for too long or too short of a duration (Bustos et al., 2009; Lee et al., 2006). A cue that is presented for too short of a time will not activate reconsolidation, but a cue that lasts too long will begin extinction, and attempts to directly disrupt reconsolidation (i.e., through pharmacological intervention) after the cue will block consolidation of the extinction memory instead. The length of time the cue must be presented to the subject is believed to vary based on the age and strength of the consolidated memory. Older memories have been more thoroughly consolidated into LTM and are more likely to have experienced greater LTP (Frankland et al., 2006). These memories are resistant to destabilization unless the activation cue is presented for a longer period of time (Frankland et al., 2006). Stronger memories also require longer activation cue durations, although some studies
have shown that strongly trained memories become more susceptible to destabilization over time (Frankland et al., 2006; Robinson & Franklin, 2010). Memories that have been strongly trained, as traumatic memories are believed to be, have experienced considerable LTP even if they are more recent (Suzuki et al., 2004). Using a contextual fear conditioning paradigm followed 24-hours later by systematic adjustment of activation cue lengths prior to administration of protein inhibitors, animal models have determined that an activation cue for a remote or strongly trained memory should take approximately 10 minutes. Shorter cues (i.e., 0, 1, 3, or 5 minutes) were shown to be less effective at initiating reconsolidation processes for these memories, as demonstrated by return of fear when the mice were re-exposed to the training context. Longer cues (i.e., 30 minutes) engaged extinction processes instead, resulting in a decrease in the fear response over the course of the cue but impaired retention of the new safety information 24-hours later (Suzuki et al., 2004). Research into the boundaries of activation cue duration in humans has yet to be done.

Reconsolidation of remote and strongly trained memories can also be triggered by exposure to novel stimuli during memory retrieval. Winters et al. (2009), used the spontaneous object recognition paradigm for rats, in which rats are allowed to explore two objects in opposite arms of a Y-shaped apparatus and later have to choose between one of the familiar objects and a novel object. In this study, mice were released into the apparatus in order to explore the two stimuli. Later, a short (~2 minute) memory activation session was conducted. In the activation session, rats were injected with an NMDA-receptor antagonist and released back into the apparatus either in the exact same context as the learning phase, or a context that was similar except for the addition of a Styrofoam floor insert that extended into each arm of the apparatus.
Twenty-four hours later, all rats were placed back into the apparatus in the original context, with one of the familiar stimuli in one arm of the maze and a new stimulus in the other arm. Reconsolidation interference was determined by the ratio of time the rats spent exploring the familiar stimulus compared to the novel stimulus. Results from the study showed that the experience of the novel context during the activation phase predicted the rats spending equal amounts of time exploring the familiar vs. the novel stimulus in the later trial. These findings suggest that the novel context during the activation trial initiated reconsolidation interference of the memory of the familiar stimulus. These findings were demonstrated even when the memory was strong (the learning session was conducted three times prior to the activation trial) or if the memory was remote (the interval between the learning and activation sessions was 48 hours). Similar results were not found in rats that did not experience the novel stimulus. These findings are similar to studies with humans that show that reconsolidation interference is facilitated by introducing new information during memory activation that contradicts with the information in the consolidated memory (Sevenster et al., 2014).

It has been theorized that memory reconsolidation is a natural memory update mechanism, so introducing novel or contradictory information during memory activation may trigger the process (Díaz-Mataix et al., 2013; Sevenster et al., 2013). This theory is supported by studies that show that reconsolidation interference does not occur when the activation cue for a lab-trained fear memory is exactly the same as a trail of fear conditioning (i.e., the activation cue includes both the CS and the CR; Forcato et al., 2008; Morris et al., 2006; Pedreira, Pérez-Cuesta, & Maldonado, 2004). On the contrary, it is believed that it is the new information of the CR not occurring with the CS that triggers the reconsolidation process (Forcato et al., 2008).
Research has also shown that memory reconsolidation does not occur after novel information relevant to the original memory has been presented multiple times (Rodriguez-Ortiz, De la Cruz, Gutiérrez, & Bermudez-Rattoni, 2005). In this study, the effect of anisomycin facilitated reconsolidation interference was strongest when novel information was presented. However, when anisomycin was administered after the new information had been presented multiple times so that learning had reached an asymptote, reconsolidation was no longer triggered by memory retrieval and the consolidated memory remained intact (Rodriguez-Ortiz et al., 2005).

The procedures taken to activate a memory cannot present information that is too indirectly related to the targeted memory. A study by Dębiec, Doyère, Nader, and LeDoux (2006) created an associated memory network in rats using second-order fear conditioning. This type of fear conditioning begins by creating a learned association between a stimulus (CS1) and a response (CR), then creates a further association between CS1 and a second stimulus (CS2). In this way, a direct association is formed between CS1 and CR, and an indirect association is formed between CS2 and CR. Results indicated that memory activation of the CS1-CR association and subsequent reconsolidation blockade disrupted only that association, without affecting the CS2-CR association. These findings demonstrate that, in order to attenuate an entire associative memory network, each individual memory needs to be activated and have its reconsolidation disrupted, but when targeting a single memory with reconsolidation interference, other related memories will not become impaired (Deębiec et al., 2006).

Reconsolidation Interference as a Potential PTSS Treatment

Research has examined memory consolidation as a potential target of interventions to prevent the development of PTSD, however, interfering with the initial consolidation of a
traumatic memory has limitations. The issues of resources and timing make targeting consolidation extremely difficult in many cases. Memory consolidation occurs immediately following an event, so targeting consolidation of a traumatic memory would require the resources to provide treatment to people within days of a traumatic event. For individual traumatic events such as rape, providing immediate mental health care can be problematic as the victim may not seek out help until after the memory has consolidated (Campbell, Wasco, Ahrens, Sefl, & Barnes, 2001; Williams, 1984). For large scale traumatic events such as natural disasters, the resources required for mass interventions for the entire affected population may not be available (World Health Organization, 2003). These logistical issues make blocking memory consolidation impractical as a measure to prevent the development of PTSD.

Even if the necessary resources were available promptly after a traumatic event, research has shown that immediate interventions may not actually be beneficial to the client. One study by Schiller et al. (2008), tested the effectiveness of consolidation interference of fear memories in human subjects. Participants were first conditioned to fear a specific stimulus by pairing its presentation with a mild electrical shock to the wrist, then that fear was extinguished during the consolidation window. Fear response, measured by skin conductance, was significantly different from zero immediately following conditioning and at the beginning of extinction. At the end of extinction training, the fear response was no longer significantly different. This demonstrates that fear of the stimulus was learned and successfully extinguished. One day later, participants returned to assess for spontaneous recovery of the fear response. Comparing responses from the end of extinction training to the responses from the test for spontaneous recovery resulted in a significant difference between the two, demonstrating that intervention during initial fear
memory consolidation did not interfere completely with the consolidation of the memory. Instead, the intervention merely engaged extinction mechanisms.

Other studies have shown that immediate treatment following a traumatic event may actually be detrimental to a person’s mental health. Using benzodiazepine to limit memory consolidation following trauma has been shown to increase the incidence rate of PTSD in trauma survivors (Gelpin, Bonne, Peri, & Brandes, 1996). This increase in PTSD symptoms has also been linked to using Critical Incidence Stress Debriefing (CISD) immediately following a traumatic event (Bisson, Jenkins, Alexander, & Bannister, 1997; Wei, Szumilas, & Kutcher, 2010). It is possible that CISD interferes with the initial consolidation of a traumatic memory, which may disrupt natural recovery and exacerbate the development of PTSD symptoms (McNally, Bryant, & Ehlers, 2003). Considering that pharmacological and psychotherapeutic intervention during traumatic memory consolidation may be damaging to victims of trauma, developing an intervention that utilizes reconsolidation mechanisms after PTSD symptoms have developed may be a safer and more beneficial strategy.

Research into interfering with reconsolidation mechanisms in fear memories often uses a pharmacological blockade of reconsolidation (Alberini & LeDoux, 2013; Brunet et al., 2008; Muravieva & Alberini, 2010; Nader et al., 2000; Tronson et al., 2006; Wood et al., 2015). Research has produced mixed results with using drugs like propranolol to target fear memories and it has been suggested that pharmacological intervention is not capable of addressing the complexities of real traumatic memories (Muravieva & Alberini, 2010; Wood et al., 2015). Utilizing behavioral techniques to engage the reconsolidation process allows for more flexibility to personalize treatments for individual differences in traumatic experiences and PTSD.
presentation. Research has shown that behavioral interventions are effective at targeting fear memories and the boundaries under which these interventions may be successful have been outlined (Björkstrand et al., 2015; Bustos et al., 2009; Deębiec et al., 2006; Díaz-Mataix et al., 2013; Forcato et al., 2009; Frankland et al., 2006; Lee, 2010; Lee et al., 2006; Monfils et al., 2009; Nader et al., 2000; Oyarzún et al., 2012; Robinson & Franklin, 2010; Schiller et al., 2010; Sevenster et al., 2013, 2014; Suzuki et al., 2004; Winters et al., 2009). The most commonly used behavioral intervention for fear memories utilizes extinction paradigms during the reconsolidation window (Björkstrand et al., 2015; Monfils et al., 2009; Oyarzún et al., 2012; Schiller et al., 2010; Soeter & Kindt, 2011). Adapting current PTSD treatments that use extinction so that they incorporate memory activation and engage reconsolidation may therefore result in a highly effective intervention.
CHAPTER 2

METHODOLOGY

This study sought to translate the current reconsolidation literature into a behavioral intervention for clinical use in treating PTSS. A sample presenting with PTSS was lead through a memory activation writing task that operated within the parameters required to initiate the reconsolidation process. After activation, participants in the experimental condition were given a short break to allow reconsolidation to commence, during which they were asked to complete a cognitive distraction task. After engaging in this task, participants then engaged in extinction during the reconsolidation window. Participants in the control condition began with the memory activation task, then immediately engaged in the extinction trial, followed by the cognitive distraction task.

Hypotheses

1) Memory reconsolidation interference will lead to a greater initial attenuation of distress in the experimental condition compared to controls, as measured by changes in Subjective Units of Distress Scale (SUDS) ratings from Day 1 to Day 2.

2) Memory reconsolidation interference will lead to decreased spontaneous recovery of symptoms in the experimental condition compared to controls, as measured by change in PTSD Checklist for DSM-5 (PCL-5) scores from Day 1 to Day 2.
3) Memory reconsolidation interference will lead to decreased spontaneous recovery of intrusion symptoms in the experimental condition compared to controls, as measured by change in PCL-5 scores from Day 1 to Day 2.

4) Memory reconsolidation interference will lead to decreased spontaneous recovery of symptoms in the experimental condition compared to controls, as measured by HR and SC on Day 2.

5) Changes in cognitions will be less related to changes in PTSS for the experimental condition compared to controls, as measured by change in Posttraumatic Cognitions Inventory (PTCI) scores and PCL-5 scores from Day 1 to Day 2.

Method

Participants

Participants from this study were recruited from a mass testing pool of undergraduate students enrolled in an introductory psychology course at a large Midwestern United States university (n=40). Study participants were randomly assigned into two conditions, stratified by sex, so that the two conditions contained a proportional number of males and females. Eligibility for this study was determined by presence of PTSS, as evidenced by total scores on the PTSD Checklist for DSM-5 (PCL-5; Blevins, Weathers, Davis, Witte, & Domino, 2015; Bovin et al., 2015) during the baseline battery of questionnaires. A cutoff score of 31 to 33 is suggested as a marker of PTSD (Bovin et al., 2015). This study expected that the effects of reconsolidation interference would be present in a sub-clinical sample, so a score of 20 was used as a cutoff. This score corresponds with an average score of at least one on all of the items on the PCL-5. Many
people who experience a trauma do not develop PTSS until months after the trauma, and symptoms may begin to stabilize or dissipate 3 to 16 months after the event (McLaughlin et al., 2011; North, Kawasaki, Spitznagel, & Hong, 2004; Rothbaum, Foa, Riggs, Murdock, & Walsh, 1992). Participant eligibility was therefore limited to people who experienced a trauma between 3 and 16 months prior to testing to help ensure that the sample for this study contained participants with current PTSS. Other exclusion criteria included heart conditions that may interfere with measures of HR, such as certain arrhythmias.

To determine the sample size, a power analysis was conducted using G*Power (Erdfelder, Faul, & Buchner, 1996). Based on the results of the study by Brunet et al. (2008), an effect size of 0.92 was used. Setting alpha to 0.05 and power to 0.80, a sample size of 12 would be needed to detect an effect. Considering that an effect size of 0.92 was found with a PTSD sample, a smaller effect size is likely to be found using a PTSS sample. Considering the likelihood of a smaller effect size, as well as the fact that power analysis does not account for many factors that affect power (e.g., reliability of measures), the sample size for this study was 20 participants per condition, in order to account for any unanticipated loss of power.

Risk, Consent, and Confidentiality

Considering that there is some risk for participants to recount their previous traumatic experiences, strict consent procedures were necessary. All participants were informed that they were expected to write about their most relevant traumatic event and that they would be asked to emotionally engage with this memory. They were also informed that research assistants would be reading their scripts and recording audio of these scripts being read aloud. All data was kept
separately from identifying information, in a locked filing cabinet or password protected electronic file. Finally, arrangements were made with the Psychological Services Center for any participants experiencing significant distress to be fast-tracked into therapy services.

Measures

Outcome Measures

Post-Traumatic Stress Symptoms

The PCL-5 is a 20-item self-report measure of PTSS and symptom severity (Bovin et al., 2015). The measure assesses DSM-5 criterion A, the presence of criterion B, C, and D symptoms, the length of time that the symptoms have been present (criterion E), and the level of distress the symptoms cause (criterion F). The initial PCL was published in 1993 and contained only 17 items (Weathers, Litz, Herman, Huska, & Keane, 1993). The current version of the scale has been updated to reflect the PTSD criteria in the newest edition of the DSM (Blevins et al., 2015). Respondents are asked to rate the degree to which they have experienced each item over the last month on a scale from 0 (not at all) to 4 (Extremely; Blevins et al., 2015). The version of the PCL-5 used in this study was adapted to assess for PTSS and symptom severity over the past week, using the following prompt:

Below is a list of problems that people sometimes have in response to a very stressful experience. Please read each problem carefully and then choose one of the numbers to indicate how much you have been bothered by that problem in the past week. **In the past week, how much were you bothered by:**

Using a veteran sample, a total score of 31 to 33 has been shown to be the optimally efficient cutoff score to maximize specificity (.69) and sensitivity (.88) of PTSD diagnosis.
(Bovin et al., 2015). The PCL-5 has shown good psychometric properties in military and community populations (Armour et al, 2015; Biehn et al., 2013; Bovin et al., 2015; Liu et al., 2014), with the initial psychometric analysis demonstrating high test-retest reliability ($r=.82$), internal consistency ($\alpha=.94$), and convergent and discriminant validity ($r=.74-.85$ and $r=.31-.60$ respectively; Blevins, Weathers, Davis, Witte, & Domino, 2015). The reliability of the PCL-5 in this study was $\alpha=.91$.

Beliefs and cognitions. The Posttraumatic Cognitions Inventory (PTCI) is a 33-item questionnaire that assesses the thoughts and beliefs of people with PTSS (Foa, Ehlers, Clark, Tolin, & Orsillo, 1999). The PTCI measures three constructs: self-blame, negative cognitions about the self, and negative cognitions about the world. Items are rated on a seven-point Likert scale from 1 (strongly disagree) to 7 (strongly agree). In this study, the prompt for the PTCI was modified to address thoughts and beliefs that participants may have had in the last week:

We are interested in the kind of thoughts you may have had in the past week about your traumatic experience. Below are a number of statements that may or may not be representative of your thinking. Please read each statement carefully and tell us how much you AGREE or DISAGREE with each by putting the appropriate number between 1 & 7 in the box to the right of the statement. People react to traumatic events in many different ways. There are no right or wrong answers to these statements.

The PTCI has been found to have high internal consistency ($\alpha=.97$) as well as high test-retest reliability at one week ($r=.74$), and at three weeks ($r=.85$; Foa et al., 1999). The PTCI has also shown convergent validity with PTSD severity ($r=.79$) anxiety ($r=.75$), and depression ($r=.75$). The PTCI was 86% accurate at discriminating between participants with and without a PTSD diagnosis. The reliability of the PTCI in this study was $\alpha=.94$. 

Psychophysiological arousal. Skin conductance response (SC) and heart rate (HR) are the most commonly used psychophysiological measures in human studies of memory reconsolidation interference (Björkstrand et al., 2015; Brunet et al. 2008; Oyarzún et al., 2012; Schiller et al., 2010; Soeter & Kindt, 2011; Wood et al., 2015). In the study by Brunet et al. (2008), these two measures also showed the strongest effect sizes (d=1.23 and d=0.92, respectively), compared to electromyogram (d=0.29). Because of these findings and the preference for SC and HR in the literature, SC and HR will be used in this study to measure psychophysiological arousal in association with spontaneous recovery of fear.

Skin conductance response. Skin conductance response (SC) is a measure of changes in electrodermal conductivity that are associated with autonomic arousal (LaBar, Gatenby, LeDoux, & Phelps, 1998). SC is the most common method for measuring spontaneous recovery of fear in human studies of memory reconsolidation interference (e.g., Björkstrand et al., 2015; Brunet et al., 2008; Oyarzún et al., 2012; Schiller et al., 2010; Soeter & Kindt, 2012; Wood et al., 2015). Studies show a strong correlation between SC and emotional memory activation, as well as between SC and amgdalar function, as measured with PET or fMRI (Furmark, Fischer, Wik, Larsson, & Fredrikson, 1997; Hanmann et al., 1999; LaBar et al., 1998). These studies demonstrate that SC is a valid and reliable measure of emotional activity and arousal, and provide support for its use as a measure of fear response.

Heart rate. Heart rate (HR) is a common measure of fear response that has been reliably used for decades (Lang, Melamed, & Hart, 1970; Sartory, Rachman, & Grey, 1977). This measure is commonly used in human pharmacological studies of memory reconsolidation interference (Brunet et al. 2008; Wood et al., 2015). Research has demonstrated highly elevated
HR in people with PTSS when they are exposed to traumatic imagery (Orr, Metzger, & Pitman, 2002; Pitman, Orr, Forgue, de Jong, & Claiborn, 1987). These studies support the use of HR as a valid measure of fear response in a human PTSS sample.

**Memory activation and exposure.** The Subjective Units of Distress Scale (SUDS) was developed by Wolpe (1973) as a self-report measure of anxiety. The respondent is asked to rate their anxiety on a scale from 0 (absolutely calm) to 100 (the worst anxiety you have ever experienced; Thyer, Papsdorf, Davis, & Vallecorsa, 1984). SUDS has been shown to have concurrent validity as a measure of anxiety with HR ($r=0.39$, $p<0.05$) and hand temperature (left hand $r=0.85$, $p<0.01$; right hand $r=0.83$, $p<0.01$; Thyer et al., 1984).

**Other Measures**

**Demographics**

The demographic questionnaire assessed sex. This information was used to stratify the random assignment to the experimental and control conditions. Participants were also asked to identify their race, age, marital status, and previous mental health diagnoses. Finally, participants were asked to identify any traumatic events they have ever experienced and to identify one that currently causes them the most distress. Information collected in the demographic questionnaire was used to determine participant eligibility.

**Traumatic events.** The Life Events Checklist for DSM-5 (LEC-5) is a 15-item self-report measure of potentially traumatic events that the respondent may have experienced in their lifetime (Weathers et al., 2013). Participants are asked to respond to each item with all relevant responses that include 0 (it happened to me), 1 (witnessed it), 2 (learned about it), 3 (part of my
job), 4 (not sure). In this study, the LEC-5 was modified to assess only for events that have occurred in the past 16 months, using the following prompt:

Listed below are a number of difficult or stressful things that sometimes happen to people. For each event, **mark all relevant responses that apply to you** to indicate that:

1. it happened to you personally;
2. you witnessed it happen to someone else;
3. you learned about it happening to a close family member or close friends;
4. You were exposed to it as part of your job (for example, paramedic, police, military, or other first responder); or
5. you’re not sure if it fits.

Be sure to consider only **the past 16 months** as you go through the list of events.

The LEC-5 is an updated version of the Life Events Checklist (LEC) that is designed to better reflect DSM-5 PTSD criterion A. The LEC has demonstrated adequate temporal stability and good convergent and criterion validity (Gray, Litz, Hsu, Lombardo, 2004).

**Procedure**

Participants began by completing a battery of baseline questionnaires including the demographic questionnaire, the PCL-5, and the PTCI, in random order. Participants who scored above a 20 on the PCL-5 were randomly assigned and stratified by sex into either the experimental or control condition. Both conditions were asked to complete a total of 50 minutes of the Pennebaker writing task and 10 minutes of the distraction task.

**Memory Activation and Exposure Task**

The Pennebaker writing task asks participants to imagine the traumatic event that causes them the most distress and write about the event in as much detail as possible (Pennebaker &
The task begins with the following prompt that encourages participants to think deeply about their traumatic event and asks specifically for them to express emotional content:

I would like for you to write about your very deepest thoughts and feelings about the most traumatic experience of your entire life. In your writing, I’d like you to really let go and explore your very deepest emotions and thoughts. You might tie this trauma to your childhood, your relationships with others, including parents, lovers, friends or relatives. You may also link this event to your past, your present or your future, or to who you have been, who you would like to be, or who you are now. All of your writing will be completely confidential. Don’t worry about spelling, sentence structure, or grammar. The only rule is that once you begin writing, continue to do so until your time is up. (Pennebaker & Chung, 2011, p. 419)

In this study, participants read the prompt out loud to ensure complete understanding. For the activation task, they were asked to prepare two separate scripts, with each script addressing a different aspect of the traumatic experience. For both the activation and habituation tasks, the Pennebaker prompt was administered, as well as another prompt to encourage participants to write for the full writing time. This prompt appeared on a nearby computer screen and was present throughout the full writing time:

Please keep writing until the time is up. You can start re-writing if necessary, adding new details as needed. The main point is that you are writing the entire time and expressing your deepest thoughts and feelings.

The Pennebaker writing task is a widely used paradigm that has been shown to be a valid and reliable form of exposure (Esterling, L’Abate, Murray, & Pennebaker, 1999; Pennebaker & Chung, 2011). A study by Danoff-Burg, Mosher, Seawell, and Agee (2010) demonstrated that writing about a stressful event in an emotionally meaningful way was associated with decreases in depression and perceived stress in both expressive writing and narrative writing conditions. In a study of rape victims, it was found that participants that used a moderate level of personalization during the writing task and included greater detail showed a significant decrease.
in symptoms of social anxiety and dysphoria (Brown & Heimberg, 2001). The Pennebaker writing task has also been used successfully in a population of people diagnosed with PTSD to decrease trauma related distress and facilitate posttraumatic growth (Smyth, Hockemeyer, & Tulloch, 2008). In this study, the writing task was used to activate the trauma memory in the experimental condition and as the habituation task in the experimental and control conditions. Each participant’s writing was assessed for personalization by counting the number of self-referencing words (e.g., “I”, “my”) and emotionality based on the number of positive and negative emotion words. These assessments have been used in multiple studies to determine the degree to which participants engage in a writing task (e.g., Brown & Heimburg, 2001; Pennebaker, 1997). The total amount of time each participant writes was recorded.

**Distraction**

All participants performed a distraction task designed to fully occupy the participants’ cognitive resources, preventing them from further engaging with their traumatic memories. This task was the Multi-Source Interference Task (MSIT). Originally, the Wisconsin Card Sorting Test (WCST) was also proposed as a distraction task for this study. Only 10 minutes of distraction was required for this study and the MSIT task took 10 minutes to administer, so the WCST was deemed unnecessary and therefore was not administered. The MSIT is a task that asks participants to identify numbers and letters that are different from the others within a set (Bush & Shin, 2006). The task has been shown to produce prolonged reaction times and increased errors, suggesting it causes cognitive interference, and it has been shown to engage cortical brain regions involved in complex cognitive processing (Bush & Shin, 2006; Bush, Shin,
Holmes, Rosen, & Vogt, 2003). The WCST asks people to classify cards but does not state the classification rules (Grant & Berg, 1948). Every ten cards, the rules change and participants must discover and implement the new classification system. The WCST has widespread use as a way to engage executive functioning and cognitive control (e.g., Barceló & Knight, 2002; Nagahama, Okina, Suzuki, Nabatame, Matsuda, 2005). Since the task was only meant to be a distraction, the specific nature of the task was not thought to be important. Therefore, only the MSIT was administered for the total 10 minutes of the Distraction Phase.

**Conditions**

After the baseline questionnaires (the *Day 1 Pre-Activation Phase*), the experimental condition began by completing 20 minutes of the writing task to activate the trauma memory (the *Day 1 Activation Phase*). During this task, they prepared two scripts regarding their trauma memory, with each script addressing a different aspect of the memory. They then stopped writing and completed 10 minutes of the distraction task (the *Day 1 Distraction Phase*). After the Distraction Phase, participants completed another 30 minutes of the writing task (the *Day 1 Habituation Phase*).

Following the Day 1 Pre-Activation Phase, the control condition began with the 20-minute Day 1 Activation Phase, followed immediately by the 30 minutes of the Day 1 Habituation Phase. This task was then followed by 10 minutes of the Day 1 Distraction Phase. For the memory activation and habituation writing tasks, participants in both conditions were asked to rate their distress at the beginning and the end of each task, as well as their highest level of distress overall, using SUDS.
Follow-Ups

The follow-up sessions were conducted in the same room as the initial session. One week following the activation trial, participants returned to the lab and completed another PCL-5 and PTCI (the *Day 2 Pre-Activation Phase*). All participants were then connected to HR and SC wireless BIOPAC equipment. All participants were asked to wear a thin t-shirt. Participants were also asked to wash their hands with a non-abrasive soap.

For HR, researchers used alcohol wipes to slightly abrade and clean the left shoulder (left arm), right shoulder (right arm) and left upper quadrant of the abdomen (left leg). Once each area dried, one lead was placed on each location, so that the lead was flush with the skin. A (+-) electrode was placed on the left shoulder (left arm), a (-) electrode on the right shoulder (right arm), and a (++) electrode on the left upper quadrant of the abdomen (left leg).

For SC, researchers began by slightly abrading and cleaning participant’s distal phalanges on their second and fourth fingers of their non-dominant hand. A unibase electrolyte paste was inserted into two silver-silver chloride cup electrodes. The positive electrode was then clamped to the volar surface of the distal phalanx of the second finger. The negative electrode was clamped to the volar surface of the distal phalanx of the fourth finger. The SC and HR electrodes were connected to a wireless transmitter strapped to the participant’s non-dominant wrist. All electrodes were then calibrated.

Participants were habituated for 3 minutes. Following habituation, readings were recorded for five minutes, with the last 30s acting as baseline (the *Day 2 Baseline Phase*). Participants then listened to 30 second audio recordings of both of their scripts being read aloud (the *Day 2 Activation Phase*). These recordings were pre-recorded by a graduate research
assistant who was blind to the conditions. Each recording included 30 seconds of the graduate student reading aloud the most personal and emotional section of that participants’ scripts, as determined by the number of self-referencing and emotional words in the writing. Following the audio exposure, participants were asked to imagine their traumatic event in detail for another 30 seconds. Participants were asked to rate their distress at the beginning and the end of this test, as well as their highest level of distress overall, using SUDS.

Figure 1 illustrates the methodology.

Figure 1. Flow chart.
Expected Limitations

One expected limitation of this study was that psychophysiological measures are often uncomfortable and invasive. Since this study sought to measure changes in participants’ distress levels, using measures that increase participant distress could introduce a confound. However, psychophysiological measures such as SC and HR have been used consistently throughout the reconsolidation literature with success (Björkstrand et al., 2015; Brunet et al., 2008; Oyarzún et al., 2012; Schiller et al., 2010; Soeter & Kindt, 2012; Wood et al., 2015). In order to better compare this study with the existing literature, psychophysiological measures were incorporated as objective measures of fear response.

A second expected limitation of this study is the use of only one experimental condition. The addition of a second experimental condition containing participants with PTSS or PTSD and no co-occurring mental health diagnoses or potential diagnoses would increase the study’s internal validity while maintaining its ecological validity. While the inclusion of this extra condition would ultimately benefit this research, the amount of time required to gather the right kind and number of participants to fill this condition is beyond the scope of this study. This study was the first step in translating the current reconsolidation literature into a clinically useful protocol for the treatment of PTSS. Clinical populations often have co-occurring disorders, so testing this protocol in a similar population was the primary goal. Future research should consider the inclusion of extra experimental conditions to increase internal and ecological validity and to assess the effect of other variables on this protocol’s efficacy.
CHAPTER 3

RESULTS

Preliminary Analyses

Of the 47 participants in the experiment, seven participants had missing data due to attrition ($n = 2$), errors in data collection ($n = 4$; i.e., psychophysiological recording equipment malfunction) or ineligibility to complete the study ($n = 1$; i.e., participant did not read English). All seven of these participants were removed from the dataset. The final dataset ($n = 40$) had <1% missing data. Little’s (1988) MCAR test suggested all missing data was missing completely at random. All further data screening and analyses were conducted with this dataset. No univariate outliers (i.e., extreme values three times or greater than the interquartile range) or extreme multivariate outliers (i.e., Mahalanobis distances greater than 7.81) were identified. Multivariate normality was established by examining the normality of each independent variable (i.e., skewness and kurtosis statistics greater than 2.58) and the linearity and homoscedasticity of each linear combination of variables (i.e., scatterplots of each independent-dependent variable pair demonstrated linear distribution and constant variability). Multivariate normality was determined to be appropriate for all planned analyses. All SUDS variables demonstrated multicollinearity. Bootstrapping (1000 iterations) was used in all analyses to correct for any potential violations of the normality, homogeneity of variance, and independence of cases assumptions for ANOVA. The means, standard deviations, and correlations for all study
variables are presented in Appendix A. For all analyses, alpha level was set at .05 and two-tailed p-values are reported.

HR Correlations

Significant Correlations

Day 2 Baseline HR was significantly correlated in the expected (i.e., positive) direction with first 30-second HR during Day 2 Activation (see Appendix A). Distress at the beginning of Day 1 Habituation was also significantly correlated with Day 2 Baseline HR, but in the unexpected (i.e., negative) direction.

HR is an index that may reflect emotional arousal (Larsen, Schneiderman, & Pasin, 1986) and resting HR has been correlated with PTSS (see Bedi & Arora, 2007), so it is unexpected that a HR measurement would negatively correlate with distress. There are several possible explanations for the unexpected correlation. The most likely of these explanations are sampling error (see “Randomization Checks” below) and high variance due to low sample size ($N = 40$; Kennedy, 2005).

Non-Significant Correlations

Non-significant negative correlations were found for the HR measurements (i.e., Day 2 Baseline HR, first 30-second HR during Day 2 Activation) with Day 2 Pre-Activation intrusions, distress at the beginning of Day 1 Activation, highest distress during Day 1 Activation, highest distress during Day 1 Habituation, Day 2 Baseline distress, and highest distress during Day 2 Activation. Also, distress at the beginning of Day 1 Habituation was non-significantly correlated
with first 30-second HR during Day 2 Activation (but significantly correlated with Day 2 Baseline HR, as described above), in the negative direction. Finally, non-significant negative correlations were also found between Day 2 Baseline HR and Day 1 Pre-Activation PTSS, Day 2 Pre-Activation PTSS, and Day 2 Pre-Activation intrusions.

**SC Correlations.**

**Significant Correlations**

Day 2 Baseline SC was significantly correlated in the expected (i.e., positive) direction with first 30-second SC during Day 2 Activation. Highest distress during Day 1 Activation was also significantly correlated with Day 2 Baseline SC, but in the unexpected (i.e., negative) direction.

SC is a correlate of negative emotion and subjective arousal (Nikula, 1991), so this negative correlation was unexpected. As with the previously mentioned unexpected HR measurement correlation, the unexpected SC measurement correlation has several possible explanations, the most likely being sampling error (see “Randomization Checks” below) and high variance due to sample size ($N = 40$; Kennedy, 2005).

**Non-Significant Correlations**

Non-significant negative correlations were found for the SC measurements (i.e., Day 2 Baseline SC and first 30-second SC during Day 2 Activation) with distress at the beginning of Day 1 Activation, distress at the beginning of Day 1 Habituation, highest distress during Day 1 Habituation, Day 2 Baseline distress, and highest distress during Day 2 Activation. Also, highest
distress during Day 1 Activation was non-significantly correlated with first 30-second SC during Day 2 Activation (but significantly correlated with Day 2 Baseline SC, as described above), in the negative direction. Finally, non-significant negative correlations were also found between Day 2 Baseline SC and Day 1 Pre-Activation cognitions, Day 2 Pre-Activation PTSS, and Day 2 Pre-Activation intrusions.

**Distress Correlations**

**Significant Correlations**

All measurements of distress were significantly correlated with all other measurements of distress in the expected directions. Furthermore, although it is not necessarily expected that all measurements of distress significantly correlate with all Day 1 and Day 2 Pre-Activation measures, most of these correlations were significant and all were in the expected direction (i.e., positive). All non-significant correlations of the measurements of distress with Day 1 and Day 2 Pre-Activation measures are reported below.

**Non-Significant Correlations**

The only non-significant correlations of the distress measurements with Day 1 and Day 2 Pre-Activation measures include: distress at the beginning of Day 1 Habituation was non-significantly correlated with Day 1 Pre-Activation intrusions, Day 2 Pre-Activation intrusions, and Day 2 Pre-Activation PTSS, in the expected directions; and Day 2 Baseline distress was non-significantly correlated with Day 1 Pre-Activation intrusions and Day 1 Pre-Activation PTSS, in the expected directions.
Self-Report Questionnaire Correlations

All correlations between self-report questionnaires were significant and in the expected directions.

Paradigm Check

Change in distress from the beginning of Day 1 Activation to the highest reported during Day 1 Activation was examined to determine if the trauma memory was successfully activated. For this paradigm check, a planned contrast was conducted in the context of the mixed model ANOVA used to test the first hypothesis (the First ANOVA). For the First ANOVA, the within-subjects variable was time (distress was measured at six time points: at the beginning of Day 1 Activation, the highest during Day 1 Activation, at the beginning of Day 1 Habituation, the highest during Day 1 Habituation, at the beginning of Day 2 Baseline, and the highest during Day 2 Activation) and the between-subjects variable was condition (i.e., experimental or control). The dependent variable was distress (i.e., SUDS ratings). Results of the First ANOVA revealed a significant main effect of time such that distress increased during Day 1 Activation ($M = 61.26$), Day 1 Habituation ($M = 50.15$), and Day 2 Activation ($M = 60.15$) compared to distress measured prior to each phase ($M = 31.10$, $M = 31.77$, and $M = 22.49$, respectively), $F(5, 185) = 48.73$, two-tailed $p < .001$. There was no significant main effect of condition, $F(1, 37) = 0.87$, two-tailed $p = .358$. There was a significant time by condition interaction effect, $F(5, 185) = 6.89$, two-tailed $p < .001$. Results of the planned contrast (i.e., $[d - c] + [b - a]$) revealed a significant difference between distress at the beginning of Day 1 Activation ($M = 31.10$) and the
highest distress during Day 1 Activation \( (M = 61.26) \), \( t(185) = -9.04 \), two-tailed \( p < .001, d = 1.679 \), confirming that memory activation occurred (Appendix B).

**Randomization Checks**

**SUDS**

As a randomization check, change in distress from the beginning of Day 1 Activation to the highest during Day 1 Activation was examined by condition to determine if the control and experimental conditions activated differently. For this randomization check, a planned contrast (i.e., \( [(b - a) - (d - c)] \)) was conducted in the context of the First ANOVA (described above). The planned contrast revealed no significant difference in memory activation during Day 1 Activation between the control and experimental conditions, \( t(185) = -0.62 \), two-tailed \( p = .539 \), \( d = 0.169 \) (Appendix B).

**Self-Report Questionnaires.**

All Day 1 Pre-Activation questionnaires were examined by condition to determine if sampling error resulted in significant differences between the conditions prior to the manipulation. For the randomization checks with Day 1 Pre-Activation PTSS and Day 1 Pre-Activation intrusions, planned contrasts were conducted in the context of two mixed model ANOVAs: one used to examine the second hypothesis (for the Second ANOVA) and one used to examine the third hypothesis (for the Third ANOVA). An independent samples \( t \)-test was used for conducting the randomization check with Day 1 Pre-Activation cognitions.
First, for the Second ANOVA, the within-subjects variable was time (PTSS was measured at two time points: during Day 1 Pre-Activation and during Day 2 Pre-Activation) and the between-subjects variable was condition (i.e., experimental or control). The dependent variable was PTSS (i.e., PCL-5 total scores). Results of the Second ANOVA revealed a marginally significant main effect of time such that symptoms decreased from Day 1 ($M = 47.73$) to Day 2 ($M = 44.28$), $F(1, 38) = 3.61$, two-tailed $p = .065$; a significant main effect of condition such that the experimental condition (Day 1 $M = 51.60$ and Day 2 $M = 49.80$) had greater scores than the control (Day 1 $M = 43.85$ and Day 2 $M = 38.75$), $F(1, 38) = 4.18$, two-tailed $p = .048$; and no significant time by condition interaction effect, $F(1, 38) = 0.83$, two-tailed $p = .370$. Planned contrasts (i.e., [b-a]) revealed that participants in the experimental condition reported significantly higher Day 1 Pre-Activation PTSS ($M = 51.60$), $t(38) = 3.02$, two-tailed $p = .005$, $d = 0.517$, (see Appendix C) than the control condition ($M = 43.85$).

Second, for the Third ANOVA, the within-subjects variable was time (intrusions were measured at two time points: during Day 1 Pre-Activation and during Day 2 Pre-Activation) and the between-subjects variable was condition (i.e., experimental or control). The dependent variable was intrusions (i.e., PCL-B scores). Results of the Second ANOVA revealed no significant main effect of time, $F(1, 38) = 0.09$, two-tailed $p = .772$; a marginally significant main effect of condition such that the experimental condition (Day 1 $M = 11.90$ and Day 2 $M = 12.00$) had greater scores than the control (Day 1 $M = 9.75$ and Day 2 $M = 9.30$), $F(1, 38) = 3.49$, two-tailed $p = .069$; and no significant time by condition interaction effect, $F(1, 38) = 0.21$, two-tailed $p = .650$. Planned contrasts (i.e., [b-a]) revealed that participants in the
experimental condition reported significantly higher Day 1 Pre-Activation intrusions \( (M = 11.90), t(38) = 2.53, \text{two-tailed } p = .016, d = 0.554, \) than the control condition \( (M = 9.75) \).

Finally, Day 1 Pre-Activation cognitions were examined by condition using an independent samples \( t \)-test. Results of this \( t \)-test revealed no significant differences between conditions on Day 1 Pre-Activation cognitions, \( t(38) = 1.23, \text{two-tailed } p = .23 \).

Although the two conditions demonstrated no significant differences in memory activation during Day 1 Activation or in Day 1 Pre-Activation cognitions, the experimental condition did demonstrate greater Day 1 Pre-Activation PTSS and intrusions, compared to the control condition. Given these results, analyses reported below were repeated controlling for Day 1 Pre-Activation PTSS. Analyses did not control for Day 1 Pre-Activation intrusions, as this scale is a component of the measure used to assess Day 1 Pre-Activation PTSS.

Primary Analyses

The first hypothesis predicted that the experimental condition would demonstrate significantly less increase in distress from Day 2 Baseline to the highest distress during Day 2 Activation, compared to the control condition. Contrary to the hypothesis, a planned contrast conducted in the context of the First ANOVA (i.e., \([ ( f - e ) - ( h - g ) ] \)) revealed that the control condition experienced less increase in distress from Day 2 Baseline \( (M = 23.53) \) to the highest during Day 2 Activation \( (M = 55.00) \), compared to the experimental condition \( (M = 21.50 \text{ and } M = 65.05, \text{respectively}), t(185) = -1.81 \) (Appendix B). This difference was marginally significant, two-tailed \( p = .071, d = 0.706 \). Thus, the manipulation enhanced distress relative to controls.
The second hypothesis predicted that the experimental condition would demonstrate a significantly greater decrease in PTSS from Day 1 Pre-Activation to Day 2 Pre-Activation, compared to the control condition. Failing to support the hypothesis, a planned contrast conducted in the context of the Second ANOVA (i.e., \([a – b) – (d – c)]\) revealed no significant difference between conditions in the change in PTSS from Day 1 Pre-Activation to Day 2 Pre-Activation, \(t(38) = 0.91, \) two-tailed \(p = .370, d = 0.218\) (Appendix C).

The third hypothesis predicted that the experimental condition would demonstrate a significantly greater decrease in intrusion symptoms from Day 1 Pre-Activation to Day 2 Pre-Activation, compared to the control condition. Failing to support the hypothesis, a planned contrast conducted in the context of the Third ANOVA (i.e., \([a – b) – (d – c)]\) revealed no significant difference between conditions in the change in intrusion symptoms from Day 1 Pre-Activation to Day 2 Pre-Activation, \(t(38) = 0.46, \) two-tailed \(p = .650, d = 0.141\).

The fourth hypothesis predicted that the experimental condition would demonstrate significantly less psychophysiological responding during Day 2 Activation, compared to the control condition. Psychophysiological responding was measured by change in average HR from Day 2 Baseline to the first 30 seconds of Day 2 Activation, and by change in highest SC from Day 2 Baseline to the first 30 seconds of Day 2 Activation. For the mixed model ANOVA used to test change in HR (the Fourth ANOVA-HR), the within-subject variable was time (HR was measured at two time points: Day 2 Baseline and the first 30 seconds of Day 2 Activation) and the between-subjects variable was condition (i.e., experimental or control). The dependent variable was average HR. Results of the Fourth ANOVA-HR indicated a significant main effect of time such that HR increased from Day 2 Baseline (\(M = 76.79\)) to Day 2 Activation (\(M = \)
82.60), $F(1, 35) = 17.75$, two-tailed $p < 0.001$; no significant main effect of condition, $F(1, 35) = 0.38$, $p = .541$; and no significant time by condition interaction effect, $F(1, 35) = 0.63$, $p = .431$. Failing to support the hypothesis, a planned contrast (i.e., $[(b - a) - (c - d)]$) revealed no significant difference in change in HR between conditions, $t(35) = 0.80$, two-tailed $p = .431$, $d = -0.179$.

For the mixed model ANOVA used to test change in SC (the Fourth ANOVA-SC), the within-subjects variable was time (SC was measured at two time points: Day 2 Baseline and the first 30 seconds of Day 2 Activation) and the between-subjects variable was condition (i.e., experimental or control). The dependent variable was highest SC. Results of the Fourth ANOVA-SC indicated a main effect of time such that highest SC increased from Day 2 Baseline ($M = 12.05$) to Day 2 Activation ($M = 17.71$), $F(1, 38) = 70.83$, two-tailed $p < .001$; no significant main effect of condition, $F(1, 38) = 0.86$, $p = .359$; and no significant time by condition interaction effect, $F(1, 38) = 2.67$, $p = .110$. Failing to support the hypothesis, a planned contrast (i.e., $[(b - a) - (c - d)]$) demonstrated no significant difference in change in SC between conditions, $t(38) = -1.64$, two-tailed $p = .110$, $d = 0.331$.

The fifth hypothesis predicted that the correlation between change in PTSS from Day 1 Pre-Activation to Day 2 Pre-Activation and change in cognitions from Day 1 Pre-Activation to Day 2 Pre-Activation would be smaller for the experimental condition than for the control condition. The correlation between change in PTSS and change in cognitions for the experimental condition was not significant, $r = .12$, two-tailed $p = .618$. This correlation was also not significant for the control condition, $r = .20$, two-tailed $p = .402$. Failing to support the hypothesis, the R-to-Z transformation used to test the fifth hypothesis revealed no significant
difference between conditions in the relationship between change in PTSS and change in cognitions, $z = 0.24$, two-tailed $p = .810$.

Discussion

Research suggests that memory reconsolidation interference may be one mechanism for treating disorders involving fear memory (Brunet et al., 2008; Telch, York, Lancaster, & Monfils, 2017). These studies show that such treatment is possible with pharmacological interventions (Brunet et al., 2008), yet findings are inconsistent (Wood et al., 2015) and research has identified several factors (e.g., length of memory activation, introduction of novel information) that must be considered before a treatment targeting reconsolidation interference may be effective (e.g., Bustos et al., 2009; Frankland et al., 2006; Nader et al., 2000). A behavioral intervention that targets reconsolidation interference may provide a more effective and flexible alternative to pharmacological interventions in the treatment of highly complex fear-memory based problems, such as PTSS. This study designed and tested a behavioral protocol that targeted interference of memory reconsolidation to permanently attenuate PTSS. Results suggest that the behavioral paradigm did result in memory activation, as subjective distress significantly increased for all participants during the Day 1 Activation phase. However, considering the lack of difference between experimental conditions and the failure of the paradigm to produce significant decreases on any measure (i.e., PCL-5, HR, SC, PTCI), this paradigm may have failed to initiate reconsolidation processes. Furthermore, the subjective distress of the participants in the experimental condition marginally increased compared to controls. This finding would be expected if the activation cue initiated extinction processes rather
than reconsolidation processes, as the subsequent interference would result in interference of the extinction memory’s consolidation and therefore less symptom reduction in the experimental condition. This result further suggests that the activation cue successfully activated the memory, but failed to initiate reconsolidation processes.

The study hypothesized that: 1) memory reconsolidation interference would lead to decreased reinstatement of subjective distress compared to a traditional written exposure, 2) memory reconsolidation interference would lead to decreased reinstatement of PTSS compared to a traditional written exposure, 3) memory reconsolidation interference would lead to decreased reinstatement of intrusion symptoms compared to a traditional written exposure, 4) memory reconsolidation interference would lead to less psychophysiological reactivity during later re-exposure to trauma-relevant stimuli compared to a traditional written exposure, and 5) change in cognitions would be less related to change in PTSS following memory reconsolidation interference compared to a traditional written exposure.

Contrary to the first hypothesis, the difference between conditions in increase of subjective distress from Day 2 Baseline to highest during Day 2 Activation was marginally significant, but in the opposite direction of what was expected. It is possible that this finding is merely a random artifact; the protocol may have been ineffective and these marginally significant results may be due to chance. However, several other explanations may also account for this surprising result. A randomization check revealed that participants in the experimental condition had higher Day 1 Pre-Activation PTSS and intrusion symptoms than participants in the control condition, despite showing no differences in initial Day 1 subjective distress. It appears that through sampling error, the experimental condition participants had more severe PTSS than
those in the control condition, although both conditions had similar levels of immediate distress at the beginning of the study paradigm. Overall PTSS severity is a predictor of treatment outcome, such that individuals with more severe symptoms are more resistant to treatment (e.g., Hembree, Street, Riggs, & Foa, 2004; Van Minnen, Arntz, & Keijsers, 2002). Thus, this initial difference in PTSS represents a confound, as participants in the experimental condition may have been more resistant to the intervention than controls.

Other aspects of the study protocol may also have contributed to the marginally significant difference between experimental and control condition participants’ subjective distress. The Day 1 Activation task may have been too long. Whereas the study design intended for the experimental condition to engage in reconsolidation interference and the control condition to engage in traditional written exposure, an overly-long activation period would have resulted in traditional exposure for both conditions (Suzuki et al., 2004). If that were the case, the control condition would have undergone a typical session of written exposure while the experimental condition would have experienced an interrupted traditional exposure session. It is possible that, compared to a session of uninterrupted traditional exposure, a session of interrupted traditional exposure may have resulted in a less effective exposure session, leading to a greater increase in subjective distress from Day 2 Baseline to highest during Day 2 Activation for the experimental condition compared to controls.

Finally, the use of the MSIT as the distraction task may have inadvertently interfered with the treatment protocol. The MSIT was designed to induce activation of the dACC (Bush et al., 2003), a region of the brain involved in the processing of conflicting information (Gabbott, Warner, Jays, Salway, & Busby, 2005; Shackman et al., 2011) and error detection (e.g., Bush,
Luu, & Posner, 2000; Gehring & Fencsik, 2001; Liotti, Kothman, Jones, Peres, & Woldorff, 2001; Luu, Tucker, Derryberry, Reed, & Poulson, 2003; Pardo, Pardo, Janer, & Raichle, 1990). Considering the dACC’s role in error detection (e.g., Bush et al., 2000; Gehring & Fencsik, 2001; Liotti et al., 2001; Luu et al., 2003; Pardo et al., 1990), it is possible that taxing the dACC may have interfered with participants’ error detection ability, thus impairing experimental condition participants’ ability to recognize safety information that conflicted with their trauma memories following memory activation. This conflicting information is an important boundary condition for initiating memory reconsolidation processes (Sevenster et al., 2013; Díaz-Mataix et al., 2013). In this study, the experimental condition engaged in the memory activation task, followed by the MSIT, then 30-minutes of exposure. The control condition engaged in 50 minutes of exposure, followed by the MSIT. If the MSIT taxed error detection ability, the experimental condition participants may not have initiated memory reconsolidation processes following memory activation, and then would have simply engaged in 30 more minutes of traditional written exposure. The control condition participants would have had fifty minutes of such an exposure; perhaps enough time to develop a competing safety memory before the MSIT could influence the exposure process. The expected result from such interference would be similar to the results of the first hypothesis in this study; a greater decrease in subjective distress for the higher dose of exposure (i.e., the control condition).

Failing to support the second, third, and fourth hypotheses, there were no significant differences in HR or SC reactivity (H4), or in change in PTSS (H2) and intrusions (H3) from Day 1 Pre-Activation to Day 2 Pre-Activation. This lack of difference between conditions may also be due to the length of the activation task; if the task was too long and both conditions
actually engaged in traditional exposure processes (Suzuki et al., 2004), then the change in all outcome variables would potentially be the same across conditions.

It is also possible that the use of the written exposure task in this study was flawed. The Pennebaker writing task instructions state: *I would like for you to write about your very deepest thoughts and feelings about the most traumatic experience of your entire life* (Pennebaker & Chung, 2011). Although participants were expected to write about the traumatic experience that is most relevant to the symptoms they reported on the PCL-5, many participants may have written about some other traumatic experience due to avoidance, confusion about the definition of trauma, etc. In this way, the study protocol may have unintentionally targeted distressing memories for some participants that were not directly related to their PTSS, so that intervention would not directly lead to a decrease in their symptoms.

Finally, regarding the fourth hypothesis, there were some unexpected correlations between the HR and SC measures; namely, distress at the beginning of Day 1 Habituation was significantly correlated with Day 2 Baseline HR in the negative direction and highest distress during Day 1 Activation was significantly correlated with Day 2 Baseline SC in the negative direction. It was unexpected that measures of psychophysiological arousal would significantly and negatively correlate with measures of subjective distress (for information on the relationship between HR and distress, see Bedi & Arora, 2007; Larsen, Schneiderman, & Pasin, 1986; for SC see Nikula, 1991). It is possible that these correlations reflect measurement error for the subjective distress measure (SUDS) the Day 2 Baseline psychophysiological measures (HR and SC), or both. Such measurement error may have negatively impacted the study results by increasing Type II error.
Failing to support the fifth hypothesis, there was no significant difference between conditions in the relationship between the change in posttraumatic cognitions from Day 1 Pre-Activation to Day 2 Pre-Activation and the change in PTSS from Day 1 Pre-Activation to Day 2 Pre-Activation. This study was relatively underpowered to examine this hypothesis, indicating that these results should be interpreted with caution. However, it is possible that both memory reconsolidation interference and traditional exposure result in similar levels of change in posttraumatic cognitions. Yet considering the null findings for the other hypotheses, it may be more likely that the results regarding the fifth hypothesis are also a product of the study protocol’s failure to engage reconsolidation processes due to the several reasons discussed above. If participants in both the experimental and control conditions actually engaged in traditional exposure processes as previously described, then it would be expected that the relationship between the change in posttraumatic cognitions and the change in PTSS would be the same for both conditions.

One limitation of this study is sampling error. Participants were randomly assigned to either the experimental or control condition. Although no significant difference was found between conditions for Day 1 Pre-Activation posttraumatic cognitions, participants in the experimental condition demonstrated significantly higher scores on Day 1 Pre-Activation PTSS and intrusion measures compared to controls. This difference at Day 1 Pre-Activation may have influenced the study’s null results and may limit any interpretation of this study’s findings. This study was also conducted on a college sample, which may limit the generalizability of any conclusions drawn from these results. Finally, random assignment of participants to the conditions was not blind. A researcher not involved in data collection generated a random
sequence that resulted in equal assignment of participants to the two conditions, stratified by sex. That sequence was given to the researcher conducting the study prior to the start of data collection. That researcher followed that sequence in assigning participants’ conditions as the participants presented to the lab. Although this procedure allowed for efficient random assignment, the researcher conducting data collection was not blind to participants’ assigned conditions which could potentially introduce bias to the study.

Despite these limitations and the failure of the behavioral paradigm, this study had several strengths. The paradigm check demonstrated that memory activation did occur, suggesting that a brief written exposure can be used in the future development of PTSS treatments that use memory reconsolidation interference (see above). Also, the longitudinal and experimental nature of this study would allow for conclusions to be drawn about causal relationships for study findings, and should therefore be implemented in future iterations of this, or similar, projects. Finally, this study was one of the first to translate many of the findings from basic and animal research for clinical use. Although the findings of this study were unexpected, they provide important information for future study design during the difficult process of translational research.

PTSS is a detrimental condition and current treatments continue to be inadequate (Bass & Golding, 2012; Davidson et al., 2001; Ursano et al., 2004; Zatzick et al., 1997). Memory reconsolidation interference has promise as a treatment target that may allow for shorter, more effective intervention. The length of time required by a memory reconsolidation intervention has potential to be much shorter than current treatments, which may reduce client drop-out and the cost of treatment. The process of reconsolidation interference also precludes symptom relapse; a
problem that cannot always be prevented by traditional exposure-based treatments. This study attempted to design and validate a treatment protocol based on the memory reconsolidation literature.

Despite this study’s null findings, these results provide information that can be used to adjust and improve the reconsolidation interference protocol for future studies. Currently, no research has examined the activation task length most appropriate for activating trauma memories in humans without initiating exposure processes. Future studies could consider using several task lengths to try to understand what length may be most effective. Studies may also wish to use distraction tasks that may tax the neural areas in which reconsolidation takes place for trauma memories, such as the hippocampus and the amygdala (Dębiec et al., 2002; Schafe & LeDoux, 2000). Tasks that may target amygdalar processes such as emotion recognition (e.g., the Emotion Face Assessment Task; Stein, Simmons, Feinstein, & Paulus, 2007) or hippocampal processes such as spatial navigation (e.g., the Dead Reckoning Task in Whishaw, Hines, & Wallace, 2001; or Tetris in Holmes, James, Coode-Bate, & Deeprose, 2009) have higher potential to interfere with the reconsolidation of the trauma memory. Studies may also consider using a blind study design and a non-college sample, to prevent bias and to improve generalizability of findings, respectively. Finally, future studies may wish to use protocols that require more direct introduction of novel safety information (e.g., Imagery Rescripting in Holmes, Arntz, & Smucker, 2007). The study of memory reconsolidation is a promising direction for the future of clinical research for memory-based disorders. The results of this study should be taken under consideration for future adaptations and iterations of treatment protocols targeting memory reconsolidation interference.
REFERENCES


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APPENDIX A

MEANS AND STANDARD DEVIATION OF, AND CORRELATION AMONG, STUDY MEASURES
Means and Standard Deviations of, and Correlations Among, Study Measures

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Note: \( N = 40 \)

1\( N = 39; 2\( N = 37 \)

\* \( p < .05 \), \** \( p < .01 \)
APPENDIX B

CHANGE IN SUDS FROM PRE-ACTIVATION TO HIGHEST DURING ACTIVATION PHASE FOR DAY 1 AND DAY 2
Change in SUDS from Pre-Activation to highest during Activation phase for Day 1 and Day 2. Planned contrast for the paradigm check = [(d-c) + (b-a)], \(t(185) = -9.04\); planned contrast for the randomization check = [(b-a) - (d-c)], \(t(185) = -0.62^{ns}\); planned contrast for hypothesis 1 = [(f-e) - (h-g)], \(t(185) = -1.81^{ns}\).
APPENDIX C

DAY 1 AND DAY 2 PRE-ACTIVATION PCL-5 SCORES
Day 1 Pre-Activation PCL-5 scores were significantly different between the conditions. No significant difference was found between conditions for the change in PTSS from Day 1 Pre-Activation to Day 2 Pre-Activation.