THE EFFECT OF RAPAMYCIN PAIRED WITH TRAUMATIC MEMORY ACTIVATION ON COGNITIVE PERFORMANCE IN VETERANS DIAGNOSED WITH PTSD

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DEDICATION

I would like to express my sincere gratitude to my committee chair, Dr. Alina Surís, and committee members, Dr. Carol North and Dr. Craig Powell, for their encouragement, guidance, feedback, and expertise. I would also like to thank my family for their unwavering love and support. Finally, I would like to thank the veterans who participated in this study.

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by

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THESIS

Presented to the Faculty of the School of Health Professions

The University of Texas Southwestern Medical Center at Dallas

In Partial Fulfillment of the Requirements

For the Degree of

MASTER OF REHABILITATION COUNSELING

The University of Texas Southwestern Medical Center at Dallas

Dallas, Texas

May, 2012

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ABSTRACT

BACKGROUND: Many individuals with posttraumatic stress disorder (PTSD) experience cognitive impairment in addition to the characteristic psychological symptoms. Animal studies have shown that rapamycin, a protein synthesis inhibitor that targets the protein kinase mTOR, can prevent the reconsolidation of a reactivated fear memory, thereby reducing its emotional strength at a neurochemical level. The aim of the current study was to determine if pairing rapamycin with traumatic memory reactivation in male veterans with combat-related PTSD would lead to an improvement in cognitive performance, based on scores from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at baseline and 1-month follow-up.

SUBJECTS: A sample of 54 male veterans with combat-related PTSD receiving healthcare at a large southwestern VA medical center participated in the study.

METHODS: In a double-blind, placebo-controlled study, male veterans with combat-related PTSD were administered either a single dose of rapamycin or placebo, followed by a script-driven memory reactivation task. Measures included the RBANS, Clinician Administered PTSD Scale (CAPS), and the Quick Inventory of Depressive Symptomatology (QIDS).

RESULTS: A repeated measures ANOVA was conducted to assess the impact of two different interventions (rapamycin, placebo) on participants' scores on the RBANS, across two time periods (baseline, one-month follow-up). The main effect comparing the two type of interventions revealed no significant differences in the effectiveness of the

two interventions in the entire sample; F (1,48) = .01, p = .921, partial eta squared < .001. When the sample was limited to participants who demonstrated a clinically significant reduction (≥ 20 points) in their CAPS score, a repeated measures ANOVA revealed a significant interaction between time and treatment intervention; Wilks Lambda = .44, F (1, 13) = 16.74, p = .001, partial eta squared = .563. Pairwise comparisons showed a significant improvement between baseline and one-month follow-up on the RBANS for participants in the placebo group, mean difference = 10.00, p = .002.

DISCUSSION: Based on these results, a single rapamycin treatment does not appear to be detrimental or beneficial to cognitive performance. Furthermore, a clinically significant reduction in PTSD symptoms due to rapamycin is not associated with an improvement in cognitive performance.

Keywords: PTSD, posttraumatic, rapamycin, reconsolidation, veterans.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

CAPS – Clinician Administered PTSD Scale

LEC – Life Event Checklist

MTBI – Mild traumatic brain injury

mTOR – Mammalian target of rapamycin

PCL – PTSD Checklist

PTSD – Posttraumatic stress disorder

QIDS – Quick Inventory of Depressive Symptomatology

RBANS – Repeatable Battery for the Assessment of Neuropsychological Status

TBI – Traumatic brain injury

CHAPTER ONE

Introduction

Posttraumatic stress disorder is an anxiety disorder that may develop after an individual has been exposed to a severe traumatic event. The symptoms of PTSD are characterized by intrusive and distressing memories of the trauma, avoidance, emotional numbing, and hyperarousal. In addition to the characteristic psychological symptoms of PTSD, many of those afflicted experience cognitive impairments, especially with attention and memory. These deficits in cognition have been linked to impaired occupational and interpersonal functioning (Geuze et al., 2009).

Recent literature suggests that the emotional strength of a traumatic memory can be reduced at the neurochemical level by disrupting its reconsolidation with a protein synthesis inhibitor after the traumatic memory has been activated (Blundell, Kouser, & Powell, 2008). Rapamycin is a protein synthesis inhibitor that specifically targets the mammalian target of rapamycin (mTOR), a protein kinase that plays an important role in synaptic plasticity and fear memory consolidation and reconsolidation (Blundell, Kouser, & Powell, 2008; Casadio et al., 1999; Parsons, Gafford, & Helmstetter, 2006).

The current study is part of a larger investigation being conducted to determine if pairing reactivation of an index traumatic memory with rapamycin in veterans with combat-related PTSD will lead to a reduction of the emotional strength of that particular traumatic memory. The effect of this treatment on cognitive performance was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status at the

baseline assessment and one month after receiving treatment. The purpose of the current study is to determine if pairing reactivation of an index traumatic memory with rapamycin in veterans with combat-related PTSD will lead to an improvement in cognitive performance.

CHAPTER TWO

Review of the Literature

Posttraumatic Stress Disorder

Posttraumatic stress disorder is an anxiety disorder that may develop after exposure to a traumatic event that involves actual or potential death, injury, or threat to physical integrity, and in which the individual responds with strong feelings of fear, helplessness, or horror (DSM-IV-R, 2000). This disorder is characterized by symptoms that may include reexperiencing the traumatic event, avoidance, emotional numbing, and hyperarousal that last for at least one month and causes clinically significant distress.

When PTSD was first included in the DSM-III in 1980, PTSD was thought of as a rare disorder that was caused by "a recognizable stressor that would evoke significant symptoms of distress in almost everyone" (DSM-III, 1980). Such stressors were believed to be an atypical occurrence and, as clarified by the DSM-III-R (1987), "outside the range of usual human experience". Subsequent epidemiological studies contradicted the DSM-III-R definition of a traumatic event by showing a high prevalence of trauma exposure in the general population (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). The DSM-IV diagnostic criterion for a traumatic event was changed to "an event or events that involved actual or threatened death, or serious injury, or a threat to the physical integrity of self or others" (DSM-IV, 1994). Additionally, a subjective element was added to the criteria of a traumatic event, stating that the person's response to the event involved fear, helplessness, or horror (DSM-IV, 1994).

The majority of the population (an estimated 60.7% of men and 51.2% of women) experience at least one traumatic event during their lifetime, but only a minority

of those who experience a trauma will develop PTSD (8.2% of men and 20.4% of women) (Kessler et al., 1995). It is normal to experience changes in one's cognitions, emotions, and behavior in reaction to a trauma and most individuals eventually recover from the stress of the trauma. An individual with PTSD has been unable to recover from the stress of the trauma and continues to experience the psychological effects of the event (Yehuda, 2002).

PTSD is characterized by the onset of persistent reexperiencing of the event, avoidance, and hyperarousal symptoms following the trauma (DSM-IV-TR, 2000). These symptoms have the ability to cause intense distress and may significantly interfere with an individual's ability to function in daily life. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), a diagnosis of PTSD is met by the following criteria:

A. The person has been exposed to a traumatic event in which both of the following were present:

(1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.

(2) the person's response involved intense fear, helplessness, or horror.

B. The traumatic event is persistently reexperienced in one (or more) of the following ways:

(1) recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions.

(2) recurrent distressing dreams of the event.

(3) acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated).

(4) intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

(5) physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:

(1) efforts to avoid thoughts, feelings, or conversations associated with the trauma.

(2) efforts to avoid activities, places, or people that arouse recollections of the trauma.

(3) inability to recall an important aspect of the trauma.

(4) markedly diminished interest or participation in significant activities.

(5) feeling of detachment or estrangement from others.

(6) restricted range of affect (e.g., unable to have loving feelings).

(7) sense of foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span).

D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:

(1) difficulty falling or staying asleep.

(2) irritability or outbursts of anger.

(3) difficulty concentrating.

(4) hypervigilance.

(5) exaggerated startle response.

E. Duration of the disturbance (symptoms in B, C, and D) is more than 1 month

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

PTSD is unique among psychiatric diagnoses in that its DSM-IV-TR definition is organized around a potentially casual event: the traumatic stressor (North, Suris, Davis, & Smith, 2009). A PTSD diagnosis requires an exposure to a trauma and the subsequent development of specific symptoms that are temporally and contextually related to the trauma (North et al., 2009). An individual who displays the symptoms of PTSD without a traumatic stressor does not have PTSD. Many symptoms of PTSD are similar to those found in other psychiatric disorders, such as major depressive disorder or generalized anxiety disorder. It is the temporal and contextual linkage of symptoms to a trauma exposure that makes them a distinct disorder as defined by the DSM-IV-TR (Breslau, Chase, & Anthony, 2002). It should be noted that although PTSD symptoms must be linked to a causal traumatic event, the causal relationship between the traumatic event and the development of symptoms is complex due to different sets of risk factors for exposure and symptom development (Breslau, 2002; North et al., 2009). North et al. (2009) warned that "a definition automatically assigning causality of the ensuing syndrome to the preceding traumatic event fails to allow alternate causal possibilities,

oversimplifies relationships, and obscures the importance of scientific inquiry into causality" (p. 36).

Prevalence

An individual's chances of developing PTSD will greatly depend on the severity, proximity, and duration of the trauma (DSM-IV-TR, 2000). The highest rates of PTSD are found among those who have survived rape, military combat and captivity, and ethnic or political genocide or internment (DSM-IV-TR). The National Comorbidity Survey found the lifetime prevalence of PTSD among adult Americans to be an estimated 7.8% (Kessler et al., 1995). The lifetime prevalence was 5.0% for men and 10.4% for women (Kessler et al., 1995).

Military Prevalence

Numerous studies have examined the prevalence of PTSD in military populations during different eras. Based on interviews with a sample of 3,016 American veterans, the National Vietnam Veterans Readjustment Study (NVVRS) estimated the lifetime prevalence of PTSD to be 30.9% for men and 26.9% for women who served in the military during the Vietnam era (Kulka, et al., 1990). The prevalence of current PTSD in a sample of 11,441 veterans of the Gulf War during the period of 1995 to 1997 was reported to be 12.1% (Kang, et al., 2003). A recent study of service members who had returned from Operation Enduring Freedom (Afghanistan) and Operation Iraqi Freedom found that 13.8% screened positive for PTSD (RAND Corporation, 2008). A cross-sectional survey of veterans attending primary care clinics at four Veterans Affairs Medical Centers in 1999 found a PTSD prevalence rate of 11.5% (Magruder et al., 2005).

Course

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Course for Military/Veterans

Longitudinal studies show that the trajectory of PTSD symptoms in those who have served in the military is variable. In their study of veterans of the Vietnam era with chronic PTSD, Bremner and others (1996) showed that the onset of symptoms typically occurred at the time of the trauma. Symptoms increased during the first few years following trauma exposure and then plateaued. At this point, symptoms became chronic, with no evidence of remissions or relapses. Orcutt, Erickson, and Wolfe (2004) studied 2,949 veterans of the Gulf War and found that the course of PTSD symptoms in this sample was typically either low levels of PTSD symptoms that showed little increase in severity over time or greater initial levels of PTSD symptoms that increased significantly

over time. Typically, hyperarousal symptoms present first, followed by avoidant symptoms, and then intrusive symptoms (Bremner, et al., 1996).

Comorbidity

There is a high prevalence of comorbid psychiatric disorders among individuals with PTSD. In fact, comorbidity is said to be the rule rather than the exception for individuals with PTSD (Brady et al., 2000). The DSM-IV-TR lists panic disorder, agoraphobia, social or other phobias, obsessive-compulsive disorder, major depression, somatization disorder, and substances use disorders as comorbid psychiatric disorders found in association with PTSD. In the general population, the most prevalent lifetime psychiatric disorders comorbid with a lifetime history of PTSD are major depression, substance use disorders, conduct disorder, and anxiety disorders (Kessler et al., 1995). These disorders have a significantly higher prevalence in individuals with a lifetime diagnosis PTSD than individuals without a lifetime diagnosis of PTSD.

Comorbidity in Combat Veterans

Deering, Gloer, Ready, Eddleman, and Alarcon performed an extensive review of PTSD comorbidity literature to study patterns of comorbidity from different trauma sources (1996). They observed that combat veterans with PTSD have the highest prevalence of comorbidity. In addition, specific comorbid psychiatric disorders were found to have different rates of occurrence with combat-related PTSD than with PTSD from other traumas. For example, the rates of comorbid substance abuse with combat-related PTSD were much higher than the rates associated with noncombat-related PTSD. The comorbid psychiatric disorders with the highest prevalence among combat veterans are alcohol use disorders, major depression, drug abuse disorders, and personality

disorders in Cluster B, particularly antisocial personality disorder, but also borderline personality disorder (Deering et al, 1996; Keande & Kaloupek, 1997). Suggested causes of the higher rates of comorbidity with combat-related PTSD include cultural factors, the chronic course of the disorder, preexisting substance abuse, intensity and duration of the trauma, gender and age differences, availability of treatment medication and therapy, and different methodological approaches to research (Deering et al., 1996).

Theories of Comorbidity

The manner in which PTSD is related to comorbidities is not known. There are currently three main theoretical models to explain PTSD comorbidity (North, Suris, & Adewuyi, 2011). One such model proposes that PTSD and other psychiatric disorders are frequently seen together due to diagnostic ambiguity and overlapping diagnostic criteria (Davidson & Foa, 1991). While it is true that PTSD shares symptoms such as sleep disturbance, poor concentration, and guilt with depression and panic attacks and avoidance with other anxiety disorders, the symptoms of PTSD must be temporally or contextually related to the traumatic stressor (DSM-IV-TR, 2000). Disorders such as depression and anxiety do not require such a tie to a precipitating stressor in their diagnostic criteria. Failing to investigate whether symptoms are temporally and contextually related will result in a nonspecific and imprecise set of symptoms. This methodological shortcoming has impeded progress in understanding the relationship between symptom overlap and PTSD comorbidity (North et al, 2011).

The second model suggests that comorbid disorders arise as a consequence of PTSD and not as direct result from trauma exposure (North et al., 2011). This model would be supported by a pattern of occurrence of comorbid disorders in individuals with

PTSD, but not in trauma-exposed individuals without PTSD. For example, a study by Breslau et al. (1997) of 801 community mothers found that the risk for developing first-onset major depression following trauma exposure was limited to those who developed PTSD, thus supporting this causal model.

Many believe that this model also explains the high prevalence of alcohol and substance use disorders in individuals with PTSD. According to the self-medication hypothesis, individuals with PTSD use alcohol and/or drugs to treat the symptoms of PTSD. A general population study found that trauma exposure followed by the development of PTSD, but not trauma exposure without the development of PTSD, increased the risk for developing a drug use disorder (Breslau, Davis, & Schulz, 2003; Chilcoat & Breslau, 1998a, 1998b). In contrast, neither trauma exposure nor PTSD development was associated with developing an alcohol use disorder (Breslau et al., 2003). The survival analysis used in this study failed to examine the temporal proximity of onset of substance abuse after trauma exposure and the authors concluded that their findings did not establish a causal relationship. Research has also demonstrated that an increase in drug use disorders following the trauma exposure and the development of PTSD does not occur across all trauma types. For example, numerous studies on disaster survivors have failed to show an increase in the development of substance use disorders following exposure to disaster-related trauma (North et al., 1999; North, Hong, Suris, & Spitznagel, 2008; North, Kawasaki, Spitznagel, & Hong, 2004; North, Smith, & Spitznagel, 1994).

The final theory asserts that trauma exposure results in PTSD and the comorbid disorders, either through shared vulnerabilities to PTSD and a pattern of comorbid

disorders within the trauma-exposed individual or the broad psychopathological effects of the trauma, which would result in PTSD and additional disorders developing independently following trauma exposure (North et al., 2011). The shared vulnerability explanation would be supported by observing a typical pattern of comorbid disorders developing in individuals with PTSD while the theory that comorbid disorders arise independently would be supported by a more random pattern of comorbid disorders (North et al., 2011).

Preexisting psychopathology is a possible factor in shared vulnerability (North et al., 2011). A community sample study of 1,007 young adults found that a history of depression prior to trauma exposure increased the risk for developing PTSD more than threefold following trauma exposure (Breslau, Davis, Peterson, & Schultz, 2000). Furthermore, analysis of prospective data from a five-year follow-up period found that trauma exposure greatly increased the risk for first-onset major depression in individuals who developed PTSD. In contrast, individuals who experienced a trauma but did not develop PTSD had only a slight and insignificant increase in risk for first-onset major depression.

In summary, research supporting the theory that PTSD comorbidity is due to diagnostic ambiguity and overlapping diagnostic criteria tends to be plagued by methodologies that fail to investigate the temporal and contextual relationship between PTSD symptoms and the traumatic event (North et al., 2011). Such data does not provide an accurate picture of PTSD symptoms and cannot be used as evidence for this model. Research has shown that other psychiatric disorders frequently develop in individuals

with PTSD, but whether this development of comorbidity is due to shared vulnerabilities or as a consequence of PTSD is not clear (North et al., 2011).

Traumatic Brain Injury

Traumatic brain injury (TBI), as well as PTSD, has been described as a "signature injury" of soldiers from OEF/OIF (Stein & McAllister, 2009). In fact, TBI is the most common type of physical injury acquired by U.S. soldiers deployed to Afghanistan and Iraq (Warden, 2006). A TBI is described as a jolt, blow, or other injury to the head that disrupts the normal function of the brain (Jaffee et al., 2008). In OEF/OIF, explosion or blast injury is the most common cause of TBI (Warden, 2006). Other causes of TBI include gunshot wounds, falls, and motor vehicle crashes (Jaffee et al., 2008). The severity of a TBI may be rated as mild, moderate, or severe (Jaffee et al., 2008). Regardless of the severity of the TBI, symptoms usually fall into three categories: somatic consequences (such as headache, vision problems, fatigue, seizures, difficulty with balance, and, in more severe cases, focal neurological deficits); cognitive dysfunction (such as difficulty with attention, memory, and language and reduced processing speed); and emotions and behavior (such as depression, anxiety, irritability, impulsivity, and disinhibition) (Silver, McAllister, & Yudofsky, 2005).

Due to different screening strategies and the possibility that milder TBIs may go undetected due to more severe injury, the incidence rate of TBI is unclear (Iverson, Langlois, McCrea, & Kelly, 2009; French & Parkinson, 2008). In soldiers who were medically evacuated from OEF/OIF, 25% had received head or neck injuries (Xydakis, Fravell, Nasser, & Casler, 2005). Hoge et al. (2008) surveyed 2,525 U.S. Army infantry soldiers three to four months after a one-year deployment to Iraq and found that 4.9% of

soldiers reported injuries with loss of consciousness and 10.3% reported injuries with altered mental status.

The frequency of attacks involving explosives is thought to be significantly higher in OEF/OIF than in previous wars and advances in protective armor and medical triage have resulted in soldiers surviving attacks and injuries that would have been fatal in previous eras (Warden, 2006). The majority of TBIs in OEF/OIF are categorized as mild TBIs (MTBI), also known as concussions (McCrea et al., 2008). Studies of MTBI in civilian populations have consistently shown that most individuals recover completely after one week to three months (McCrea et al., 2005). Approximately 10 – 15% of individuals with MTBI will report chronic symptoms at one year after injury (Alexander, 1995). These symptoms, which overlap with PTSD symptoms, are referred to as persistent postconcussive syndrome (PPCS) (Stein & McAllister, 2009).

A recent study of OIF soldiers reported that 44% of soldiers with MTBI accompanied by loss of consciousness and 27% of soldiers with MTBI accompanied by altered mental status met criteria for PTSD (Hoge et al. 2008). This study is limited by its use of a screening instrument, rather than a diagnostic instrument, to assess for PTSD. This same study by Hoge et al. (2008), a cross-sectional study of Army infantry soldiers three to four months after their return from OIF, found that soldiers with a history of MTBI, especially those who experienced loss of consciousness at the time of their injury, were significantly more likely to report postconcussive symptoms and somatic symptoms, poor general health, and more work days missed. After controlling for PTSD and depression, MTBI was no longer significantly associated with these health outcomes. In a longitudinal cohort study that surveyed National Guard soldiers in Iraq one month

before returning home and twelve months later, Polusny et al. (2011) found that soldiers who reported a history of MTBI were more likely to report postdeployment postconcussive symptoms and poor psychosocial outcomes than soldiers who did not report a history of MTBI. However, after adjusting for PTSD symptoms, MTBI was no longer associated with postdeployment postconcussive symptoms or psychosocial outcomes. Instead, PTSD symptoms measured one month before returning home were a stronger predictor of postdeployment postconcussive symptoms and psychosocial outcomes. These studies further demonstrate the significant impact of PTSD on health and psychosocial outcomes, the need for proper assessment of both TBI and PTSD, and the necessity of effective PTSD treatments.

Cognitive Performance

Individuals diagnosed with PTSD frequently complain of difficulties with memory and concentration (Archibald & Tuddenham, 1965; Burstein, 1985; Gil, Calev, Greenberg, & Kugelmass, 1990). Research has provided objective evidence demonstrating that individuals with PTSD display neuropsychological deficits on standardized measures of attention, memory, and learning when compared to controls. These deficits have been found regardless of population or trauma type.

Many individuals with PTSD report difficulties with inattention. This complaint is consistent with the impaired performance (compared to controls) by individuals with PTSD on objective attentional tasks (Brandes et al., 2002; Gil et al., 1990; Gilbertson, Gurvits, Lasko, Orr, & Pitman, 2001; LaGarde, Doyon, & Brunet, 2010; Sachinvala et al., 2000; Shucard, 2008; Uddo, Vasterling, Brailey, & Sutker, 1992; Vasterling, Brailey, Constans, & Sutker, 1998; Vasterling et al., 2002; Yehuda et al., 1995). Although

numerous studies have shown attentional deficits in individuals with PTSD, studies by Neylan et al. (2004) and Golier and Yehuda (1997) did not report impaired performances on attentional tasks. Not all aspects of attention appear to be impaired. Studies have shown that individuals with PTSD demonstrate impaired performance on tasks requiring sustained attention, but no impairment on tasks requiring shifts in attention (Gil et al., 1990; Jenkins, Langlais, Delis, & Cohen, 2000; Vasterling, Brailey, & Sutker, 2000; Vasterling et al., 1998, 2002). In contrast, Golier and Yehuda (1997) did not find impairment of sustained attention. Impairments were also not reported for measures of initial attention and focus of attention (Vasterling et al., 2002, Yehuda et al., 1995).

Impaired performance on tasks of memory has also been found in individuals with PTSD (Barrett, Green, Morris, Giles, & Croft, 1996; Bremner et al., 1995; Geuze, Vermetten, de Kloet, Hijman, & Westenberg, 2008; Gil et al., 1990; Gilbertson et al., 2001; Jelinek et al., 2006; Jenkins et al., 1998; Johnsen & Asbornsen, 2008; Sachinvala et al., 2000; Vasterling et al., 1998, 2002). Exceptions to this finding include studies by Crowell, Kieffer, Siders, and Vanderploeg (2002) and Neylan et al. (2004). As with attention, the impairment does not seem to affect all aspects of memory. For example, numerous studies have found impaired performance in tasks of verbal memory (Barrett et al.,1996; Bremner et al., 1995, Geuze et al., 2008; Jelinek et al., 2006), but only a limited number have found similar impairment on measures of nonverbal memory (Jelinek et al., 2006). In fact, in their study of adult survivors of childhood abuse, Bremner et al. (1995) reported that the severity of abuse was significantly correlated with short-term verbal-recall. Dickie, Brunet, Akerib, & Armony (2008) also found that memory performance was negatively correlated with the severity of PTSD symptoms. In another example of

cognitive deficits affecting selective aspects of memory, Vasterling et al. (2002) found that individuals with PTSD demonstrate significantly impaired performances on tasks related to working memory, but did not find any impairment on tasks of memory savings.

Individuals with PTSD have also been found to have impaired performance on measures of learning (Bustamante, Mellman, David, & Fins, 2001; Geuze et al., 2008; Uddo et al., 1993; Vasterling et al., 1998, 2002; Yehuda, Golier, Halligan, & Harvey, 2004). Specifically, individuals with PTSD show significant impairment when faced with learning tasks involving retroactive interference (Bustamante et al., 2001;Vasterling et al., 1998; Yehuda et al., 1995). Retroactive interference occurs when newly learned information impedes the retrieval of previously learned information. Uddo et al. (1993) found impairment in tasks related to proactive interference, however this finding was not replicated by Yehuda et al. (1995). This type of interference results in an individual having difficulty learning new information due to previously learned and competing information. Studies by Vasterling et al. (2002, 1998) reported cognitive deficits related to initial learning. Brandes et al. (2002), and Uddo et al. (1993) also found evidence of impaired performance on tasks of verbal learning. Yehuda et al. (1995) found no cognitive impairment in the area of cumulative learning, while Bustamante et al. (2001) did find significant impairment.

Language abilities have not been studied as frequently as attention, memory, and learning. Verbal fluency, however, has been studied more extensively due to the belief that it is sensitive to prefrontal cortical dysfunction and research has found that individuals with PTSD exhibit impaired performance in this area (Bustamante et al., 2001; Koenen et al., 2001; Shimamura, 2002; Stein, Kennedy, & Twamley, 2002; Uddo

et al., 1993). Research is more robust for phonemic list generation (listing words that begin with a specific letter) than for semantic list generation (listing words that belong to a specific category) (Bustamante et al., 2001; Gil et al., 1990; Koenen et al., 2001; Stein et al., 2002; Uddo et al., 1993).

Memory Consolidation and Reconsolidation

New memories are initially in a labile state that is sensitive to disruption by distracting stimuli, injury, and pharmacological agents (Dudai, 2004). Within a short period of time, the memory is consolidated at the cellular level into a stable long-term memory (Lupien & Maheu, 2007; Nader, Schafe, & LeDoux, 2000). Consolidation is required for the long-term preservation of the memory trace (Dudai, 2004; Nader et al., 2000). Each time a memory is reactivated, it returns to a transient state of lability and becomes sensitive to disruption. Following reactivation, the memory must be consolidated again (reconsolidation) to achieve its previous stability (Lupien & Maheu, 2007).

Reconsolidation is believed to be a dynamic process in which new information from the retrieval environment is integrated into the existing memory's established synaptic network (Nader et al., 2000; Przybyslawski & Sara, 1997). Disrupting the updating process that occurs during reconsolidation prevents the memory from being restored in long-term memory (Monfils, Cowansage, Klann, & LeDoux, 2009). This changes the molecular organization of the memory trace and diminishes the strength of the memory (Duvarci & Nader, 2004; Nader et al., 2000; Monfils et al., 2009).

Beginning in the 1960's, and documented in hundreds of publications, researchers have found that administering protein synthesis inhibitors before or shortly

after training resulted in amnesia for the learned information (Davis & Squire, 1984). Administering the same treatment at a later period resulted in no amnesia. These results were consistent across species and learning paradigms. Research has also demonstrated that reactivated memories return to a labile state that is also sensitive to protein synthesis inhibitors (Nader et al., 2000; Sara 2000). These studies suggest that both consolidation and reconsolidation require a period of protein synthesis.

The Use of Protein Synthesis Inhibitors to Disrupt Fear Memory

Nader, Schafe, and Le Doux (2000) investigated whether reactivated memories require reconsolidation with protein synthesis to persist. Mice were trained using an auditory fear conditioning training model and, 24 hours later, were presented with the conditioned stimulus to reactivate the memory. Immediately after the presentation, researchers administered anisomycin, a protein synthesis inhibitor, or vehicle into the lateral and basal nuclei of the amygdala of the mice. The combination of memory reactivation and anisomycin yielded a dose-dependent decrease in freezing when the mice were again presented with the conditioned stimulus 24 hours later. This reduction in freezing was not seen when the memory of the auditory fear training was not reactivated before the administration of anisomycin.

When the anisomycin was administered six hours after instead of immediately following memory reactivation, the anisomycin had no effect. Next, the researchers increased the window between training and reactivation from one day to 14 days. This resulted increased freezing during the reactivation procedure. Mice that were immediately administered anisomycin displayed significantly less freezing when re-exposed to the conditioned stimulus.

Nader, Schafe and Le Doux interpreted these findings as suggesting that the reactivation of a consolidated fear memory, even a well consolidated fear memory, puts it in a labile state that has to be restabilized through reconsolidation requiring protein synthesis for the memory to persist. They also concluded that protein synthesis during reconsolidation takes place during a specific time window, just as in consolidation, and thus, disrupting reconsolidation using protein synthesis inhibitors is only effective during this time window.

Parsons, Gafford, and Helmstatter (2006) used similar model of auditory fear conditioning training paired with administration of a protein synthesis inhibitor into the amygdala. In this study, however, rapamycin, an inhibitor of mTOR-regulated protein synthesis, was used instead of anisomycin. The researchers found that administering rapamycin to the rats after initial training had a dose-dependent effect on the consolidation of the fear memory when animals were tested with the auditory conditioned stimulus and training context. To determine whether rapamycin was disrupting memory through selective inhibition of protein synthesis or shutting down overall protein synthesis, they observed the effect of rapamycin on local [C14]-leucine incorporation in the amygdala and reported only a 12% reduction compared to the control. They concluded that using rapamycin to obstruct the mTOR pathway inhibits the translation of a distinct subset of pertinent transcripts rather than causing a global obstruction of protein synthesis.

The Mammalian Target of Rapamycin (mTOR)

The synapse is “the essential cellular unit of memory” and the site of neuronal communication (Hoeffer & Klann, 2009). Long-term memory storage involves cellular

gene expression, changes in protein synthesis, and the growth of new synaptic connections (Bailey, Bartsch, & Kandel, 1996).

Protein synthesis requires transcription (the synthesis of mRNA from a DNA template) and translation (a process in which ribosomes synthesize proteins using the mature mRNA transcript produced during transcription). The mammalian target of rapamycin (mTOR) kinase regulates a subset of protein synthesis in neurons by controlling translation through the phosphorylation of p70 ribosomal S6 protein kinase (p70S6K), eukaryotic initiation factor 4E-binding protein (4E-BP), and other intracellular targets (Burnett, Barrow, Cohen, Snyder, & Sabatini, 1998; Raught, Gingras, & Sonenberg, 2001). The substrates p70S6K and 4E-BP are utilized in the initiation of protein translation (Hay & Sonenberg, 2004).

Synaptic plasticity is a physiological process in which the strength of synaptic connections changes to due to specific patterns of neural activity (Martin, Grimwood, & Morris, 2000). Synaptic plasticity is believed to be the process by which memory traces are consolidated and reconsolidated (Martin et al., 2000). According to the synaptic plasticity and memory hypothesis proposed by Martin et al. (2000), "activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation, and is both necessary and sufficient for the information storage underlying the type of memory mediated by the brain area in which that plasticity is observed" (p.650). Casadio et al. (1999) first demonstrated that the mTOR signaling pathway is involved in synaptic plasticity by using rapamycin, an inhibitor of mTOR activity, to prevent long-term facilitation (LTF) in Aplysia sensory neurons. Rapamycin has also been shown to prevent

LTF at the neuromuscular junction in crayfish and long-term potentiation (LTP) in the rat hippocampus (Beaumont, Zhong, Fletcher, Froemke, & Zucker, 2001; Tang et al., 2002).

Rapamycin

Rapamycin is a macrocyclic antiobiotic produced by a strain of the soil bacterium *Streptomyces hygroscopicus*. This strain of bacteria is indigenous to Easter Island, also known as Rapa Nui (Sehgal, Baker, & Vezina, 1975). Marketed under the trade name Rapamune, rapamycin was approved by the FDA in 1990 as an immunosuppressant for use after renal transplantation. It is also being investigated as a treatment for numerous types of cancer, cardiovascular disease, age-related diseases, autoimmune disorders, diabetes, obesity, and neurological disorders (Chen et al., 2007; Dann, Selvaraj, & Thomas, 2007; Tsang, Qi, Liu, & Zheng, 2007; Vignot, Faivre, Aguirre, & Raymond, 2005).

Rapamycin inhibits protein synthesis regulated by mTOR by forming a complex with the intracellular protein FKBP12 that binds to sites in the N-terminal domain in mTOR kinases and resulting in inhibition of enzymatic activity (Swiech, Perycz, Malik, & Jaworski, 2008). By inhibiting mTOR kinase activity, the signal to the downstream messengers S6K1 and 4E-BP1 is blocked, preventing the translation of crucial mRNAs needed for the progression of the cell cycle (Raught, Gingras, & Sonenberg, 2000).

Disrupting Fear Memories with Rapamycin

Blundell, Kouser, and Powell examined the role of mTOR in traumatic memory reconsolidation in their 2008 study. In this study, mice were systemically administered rapamycin during a range of time points relative to contextual fear conditioning training and fear memory reactivation. Behavioral freezing was used as a

measure of fear learning and memory. Compared to a vehicle control group, mice treated with rapamycin thirty minutes before training or immediately after training showed significantly decreased memory when re-exposed to the training environment. This finding supports the conclusion that rapamycin-induced systemic inhibition of the mTOR pathway significantly decreases contextual fear memory consolidation.

To reactivate contextual fear memory, mice were trained using the contextual fear conditioning model and re-exposed to the training environment 24 hours later. After successful reactivation, mice were immediately administered rapamycin. After 24 hours, mice treated with rapamycin demonstrated a significant reduction in fear memory compared to the control group, demonstrating that rapamycin-induced systemic inhibition of the mTOR pathway significantly decreases contextual fear memory reconsolidation. In addition, the reduction of contextual fear memory was found to be dependent on the reactivation of the fear memory and not due solely to the administration of rapamycin. Furthermore, mice treated with a single administration of rapamycin continued to have a significant reduction in contextual fear memory 21 days after the reactivation and treatment compared to vehicle-treated mice.

To determine if the reduction in fear memory was due to augmenting extinction or disrupting reconsolidation, researchers trained and reactivated the fear memories for mice systemically treated with rapamycin, anisomycin (another protein synthesis inhibitor), or vehicle, and introduced a subthreshold reminder shock four hours after reactivation. Previous research has demonstrated that extinction of a fear memory, but not the effects of disrupted consolidation, can be reversed by using a “reminder shock” that is below the threshold of the original fear conditioning (Cai et al., 2006; Duvarci & Nader,

2004). Twenty-four hours after the reminder shock, rapamycin- and anisomycin-treated mice showed no signs of being affected by the reminder shock. The similarity of the effects of rapamycin and anisomycin and the ineffectiveness of the reminder shock led Blundell et al. (2008) to conclude that rapamycin acts on reconsolidation rather than extinction.

This study demonstrated that rapamycin-induced systemic inhibition of mTOR following reactivation of a fear memory reduces fear memory reconsolidation and the strength of that memory in a lasting manner. The findings of this study offer a rodent model, based on inhibition on reconsolidation, for treating of anxiety disorders in humans.

Rationale for the Current Study

In studies of Axis I psychiatric disorders, including PTSD, researchers have found that greater cognitive impairments were associated with more severe psychiatric symptoms and functional impairments (Geuze et al., 2009; Green, Kern, Braff, & Mintz, 2000; Kalechstein, Newton, & van Gorp, 2003; Marvel & Paradiso, 2004; Twamley et al., 2002). For example, numerous studies have found PTSD symptom severity to be predictive of reduced performance on measures of memory (Bremner et al., 1993; Dickie, Brunet, Akerib, & Armony, 2007; Gilbertson et al., 2001). In addition, objective memory performance has been found to be a reliable predictor of current social and occupational functioning of individuals diagnosed with PTSD (Geuze et al., 2009).

Only a few studies have examined whether a reduction in the severity of PTSD symptoms is accompanied by an improvement in cognitive performance. The majority of these studies have utilized medications for treatment. For example, Vermetten et al.

(2003) assessed the effect of 9 – 12 months of treatment with paroxetine, an SSRI, on PTSD symptoms, declarative memory, and hippocampal volume in 23 individuals with PTSD. PTSD symptoms were evaluated using the Clinician Administered PTSD Scale (CAPS) and declarative memory was assessed using the logical memory and figural memory subtests of the Wechsler Memory Scale-Revised and the verbal and visual components of the Selective Reminding Test. The paroxetine treatment led to a mean 54% reduction in PTSD symptoms and significant improvements on measures of verbal declarative memory. Researchers also found a significant increase in hippocampal volume, although these changes were not associated with a reduction of PTSD symptoms as measured by the CAPS. Limitations of this study include the absence of a control group.

A pilot study by Heresco-Levy et al. (2002) investigated the use of D-cylcoserine, an NMDA receptor agonist, in treating chronic PTSD. The study was designed as a double-blind, placebo-controlled, cross-over trial. Psychological symptoms were assessed using the CAPS, the Mississippi Scale for Combat-Related PTSD - civilian version, the Hamilton Depression Rating Scale, and the Hamilton Rating Scale for Anxiety. Neurocognitive tests included the Wisconsin Card Sorting Test, the Hebrew version of the Auditory Verbal Learning Test, and the Benton Visual Retention Test. In both the treatment and placebo groups, subjects showed significant improvements in numbing, avoidance, and anxiety symptoms. The treatment group also demonstrated a significant reduction in perseveration error scores on the Wisconsin Card Sorting Test.

Battista et al. (2007) conducted a pilot study to examine the effect of memantine, an NMDA receptor antagonist, on the psychiatric and cognitive symptoms associated

with PTSD. PTSD symptom severity was assessed with the CAPS and cognitive performance was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Depression severity was also assessed using the Beck Depression Inventory-II (BDI-II). No inferential statistics were appropriate for the data set due to the small sample size (n = 4), but an examination of the means from baseline assessment to 12-week outcome demonstrated a mean reduction of 8.3 points in hyperarousal symptoms on the CAPS (SD = 11.5) and a mean improvement of 19.3 points in delayed memory on the RBANS (SD = 2.9). Scores on the BDI-II showed an average decrease of 9.8 points from baseline to outcome. Limitations of this study include the small sample size and lack of control group.

Bremner et al. (2005) investigated the use of phenytoin, an anticonvulsant, to reduce PTSD symptom severity while improving memory function and increasing hippocampal volume. In an open label trial, nine participants were administered phenytoin for three months and dosage was adjusted to be within the therapeutic range used in epilepsy treatment. PTSD symptoms severity was measured before and after treatment with the CAPS. Current depressive symptoms and state anxiety were also measured with the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A). Neuropsychological measures included the Gordon Box test, Trails Test, Parts A and B, the Selective Reminding Test (SRT), and paragraph recall utilizing methods similar to the Wechsler Memory Scale. After three months, treatment with phenytoin resulted in a significant improvement in PTSD symptoms, a significant 6% increase in right whole brain volume, including a nonsignificant 5% increase in right hippocampal volume. In contrast to the previous

studies mentioned, there were no significant changes in memory or cognition after treatment. Interestingly, improvements on Trails A and Trails B were correlated with increases in right hippocampal volume. Limitations of this study include the small sample size, lack of control group, and open-label study design.

An exploratory study by Walter, Palmieri, and Gunstad (2010) examined whether 15 women with PTSD who were treated with trauma-focused individual therapy experienced an improvement in executive function. Participants were treated with 10 sessions of prolonged exposure therapy, 12 sessions of cognitive processing therapy, or 12 sessions of non-manualized trauma focused therapy. PTSD symptom severity was assessed with the Post-Traumatic Symptom Scale-Self-Report (PSS-SR) and executive functioning was evaluated using the Boston Qualitative Scoring System for the Rey-Osterrieth Complex Figure Task, condition 4 of the Delis-Kaplan Executive Function System Trail Making Test Letter-Number Sequencing, and the Stroop Color and Word Test. The Beck Depression Inventory-II and the State-Trait Anxiety Inventory were also administered. Analysis of the data from the baseline assessment and 3-month follow up assessment show a significant omnibus effect for improvement in psychological symptoms and a medium-sized effect for improvement on measures of cognitive flexibility/set-shifting and organization/planning. Limitations of this study include a lack of random assignment and the absence of a control group.

Although most of these studies were preliminary and did not have large sample sizes or control groups, their results were promising. Based on these findings, if a single systemic dose of rapamycin combined with traumatic memory reactivation is able to

reduce PTSD symptom severity, it is logical to expect an improved performance on neurocognitive measures.

Objectives of the Current Study

This study is part of a larger investigation being conducted to determine if pairing reactivation of an index traumatic memory with an mTOR antagonist (rapamycin) in men with combat-related PTSD will lead to a reduction of the emotional strength of that particular traumatic memory. The hypotheses of the larger study are:

I. Traumatic memory reactivation paired with a single dose of rapamycin will decrease objective and physiological measures of stress and self-report of stress during replay of the traumatic memory, relative to subjects receiving placebo.

II. Pairing administration of rapamycin with traumatic memory reactivation will decrease PTSD symptoms one month and three months later, relative to patients receiving placebo.

The purpose of this study is to determine if pairing reactivation of an index traumatic memory with an mTOR antagonist (rapamycin) in men with combat-related PTSD will lead to an improvement in cognitive performance. The hypotheses for this study are:

I. In a sample of male veterans with combat-related PTSD, participants who are treated with a single dose of rapamycin paired with traumatic memory reactivation will show a greater improvement in their cognitive performance, as measured by the RBANS at baseline and one-month follow-up, than participants who are treated with placebo paired with traumatic memory reactivation.

    a. In a sample of male veterans with combat-related PTSD, veterans from the OEF/OIF era who are treated with a single dose of rapamycin paired

b. with traumatic memory reactivation will show a greater improvement in cognitive performance, as measured by the RBANS at baseline and one-month follow-up, than veterans from the Vietnam era who are treated with a single dose of rapamycin paired with traumatic memory reactivation.

c. In a sample of male veterans with combat-related PTSD, veterans from the OEF/OIF era who are treated with a single dose of rapamycin paired with traumatic memory reactivation will show a greater improvement in cognitive performance, as measured by the RBANS at baseline and one-month follow-up, than veterans from the OEF/OIF era who are treated with placebo paired with traumatic memory reactivation.

II. In the rapamycin-treated sample, a reduction in PTSD symptoms, as measured by the CAPS at baseline and one-month follow-up, will be associated with an improvement in cognitive performance, as measured by the RBANS at baseline and one-month follow-up. A decrease in CAPS scores from baseline to one-month follow-up will be associated with an increase in RBANS scores from baseline to one-month follow-up.

a. In the rapamycin-treated sample, the reduction in PTSD symptoms, as measured by the CAPS at baseline and one-month follow-up, and improvement in cognitive performance, as measured by the RBANS at baseline and one-month follow-up, will be greater in OEF/OIF veterans than in Vietnam veterans.

III. In the rapamycin-treated sample, a reduction in depression severity, as measured by the QIDS at baseline and one-month follow-up, will be associated with an improvement in cognitive performance, as measured by the RBANS at baseline and one-month follow up. A decrease in QIDS scores from baseline to one-month follow-up will be associated with an increase in RBANS scores from baseline to one-month follow-up.

    a. In the rapamycin-treated sample, the reduction in depression symptoms, as measured by the QIDS at baseline and one-month follow-up, and improvement in cognitive performance, as measured by the RBANS at baseline and one- month follow-up, will be greater in OEF/OIF veterans than in Vietnam veterans.

CHAPTER THREE

Methodology

Study Design

The larger study was conducted as a double-blind randomized clinical controlled trial. All participants attended five sessions conducted over a time period of approximately four months. All sessions took place at the Dallas VAMC.

Participants

Fifty-four male veterans with military-related PTSD were recruited for the study through clinical referrals from Mental Health Trauma Services and two general mental health treatment teams at a large southwestern VA medical center. Approval by the Institutional Review Board (IRB) was acquired prior to recruitment. Potential participants were identified though clinician referrals from trauma clinics, visiting veterans groups, and IRB-approved advertising. Eligibility for the study was determined by conferring with the referring clinician and/or reviewing the veteran's electronic medical records (which was allowed because of an approved HIPAA waiver). If he was eligible, the veteran was contacted to determine his interest in participating in the study. If interested, the veteran was called by a study coordinator to review the purpose and structure of the study. The study coordinator then asked the veteran permission to ask screening questions or scheduled an appointment for an initial screening. If the veteran met the study's screening criteria and was interested in participating in the study, an informed consent appointment was scheduled.

Inclusion criteria included:

1. Male veteran

2. Diagnosis of PTSD related to combat

Exclusion criteria included:

1. Hypersensitivity to rapamycin
2. Organic Brain Damage (including unresolved TBI sequela. Cognitive impairment was assessed with the RBANS during the baseline assessment and a score that was two standard deviations or more below the average excluded the participant from the study).
3. Current immunosuppressant therapy
4. Prominent suicidal or homicidal features
5. Medical conditions that preclude the administration of rapamycin, such as systemic infections, congestive heart failure, renal failure, or hepatic failure.

Measures

Demographic Questionnaire

During the baseline assessment, participant self-reported demographic information was collected using the Demographic Questionnaire. Information gathered included: residence, marital status, education, occupation, employment status, service branch, number of tours, dates of active duty, length of combat exposure or involvement, service connection, and PTSD service connection status.

Clinician Administered PTSD Scale

The Clinician Administered PTSD Scale for the DSM-IV (CAPS) was administered to participants at baseline to measure pre-treatment PTSD symptom

severity. The CAPS was administered again during the 1- and 3-month follow-up appointments to assess any post-treatment changes in symptoms. Developed by Blake et al. in 1995, the CAPS is a 20-item structured clinical interview that corresponds with DSM-IV-TR PTSD criteria. It is used extensively in both clinical and research settings. The CAPS measures the frequency and intensity of the DSM-IV-TR's 17 symptoms of PTSD using a behaviorally anchored 5-point rating scale. Frequency ratings range from 0 ("never") to 4 ("daily or almost daily) and intensity ratings from 0 ("none") to 4 ("extreme"). The frequency and intensity scores may be added to generate a 9-point (0-8) severity rating for each symptom. Summing the severity scores for the 17 symptoms produces a continuous measure of overall PTSD severity ranging from 0 to 136. When the CAPS is used to establish a diagnosis of PTSD, the most commonly used scoring rule is the original F1/I2 rule, whereby a symptom is considered present when there is a frequency score of 1 or more and an intensity score of 2 or more (Blake et al., 2000). Diagnostic criteria for PTSD are met when an individual experienced a traumatic event and responded to the event with either intense fear, helplessness, or horror (Criterion A), has at least one re-experiencing symptom (Criterion B), has at least three avoidance and numbing symptoms (Criterion C), and has at least two hyperarousal symptoms (Criterion D). In addition, the symptoms must be present for a minimum of one month (Criterion E) and result in significant distress or impairment in functioning in social, occupational, or other important areas of life (Criterion F). The presence of Criterion A is established by administering the Life Events Checklist to identify traumatic experiences and querying

up to three experiences to determine that the trauma involved a life threat, serious injury, or threat to physical integrity, and the individual reacted with intense fear, helplessness, or horror. The CAPS has demonstrated a test-retest reliability ranging from .90 to .98 and internal consistency of .94 for all seventeen items (Blake et al., 1995). The CAPS total severity score was also found to be strongly correlated with other measures of PTSD, such as the Mississippi Scale for Combat–Related PTSD (Keane, Caddell, & Taylor, 1988; r = .91) and the PK scale of the MMPI-2 (Keane, Malloy, & Fairbank, 1984; r = .77) (Blake et al., 1995).

Repeatable Battery for the Assessment of Neuropsychological Status

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998) was administered to participants at baseline to measure pre-treatment cognitive functioning. If an individual obtained a Total Score that was two standard deviations or more below the average, he was not enrolled in the study. The test was administered again during the one-month follow up appointment to assess for post-treatment changes in cognitive functioning. The RBANS is a neuropsychological screening test composed of 12 subtests that are combined to calculate five index scores (immediate memory, visuospatial /constructional abilities, language, attention, and delayed memory; See Tables 1 and 2). The five index scores are summed to produce a RBANS total score, which is a measure of overall cognitive functioning. Each score is expressed as a standard score with a mean of 100 and a standard deviation of 15 based on normative data from a study group of 540 subjects. These subjects ranged in age from 20 – 89 years and were matched to the U.S. Census on sex, ethnicity, and level of education.

The RBANS has two alternate forms (A and B) with different test items that allow for repeated testing with reduced practice effect. The two forms are psychometrically equivalent. The average reliability coefficients for RBANS are all in the .80s and it has been shown to have good validity (Randolph, 1998).

Recent research has demonstrated the solid clinical utility for the RBANS in the neuropsychological assessment of TBI. Each of the individual subtests demonstrated good construct validity and most index scores, with the exception of the language and attention indexes, demonstrated good to strong internal consistency (McKay, Casey, Wertheimer, & Fichtenberg, 2007). These findings for the language and attention indexes were expected due to the fact that the tasks of their subtests are typically insensitive to TBI sequelae (McKay et al., 2007). The total score index displayed high sensitivity and specificity, while the domain-specific index scores showed modest sensitivity and high specificity (McKay, Wertheimer, Fichtenberg, & Casey, 2008).

Although research has not investigated the psychometric properties of the RBANS in military samples, the measure has been frequently used in studies with participants recruited exclusively from veteran populations. One of these studies examined cognitive functioning in OEF/OIF burn patients with MTBI (Cooper et al., 2010). Another study examined cognitive functioning in veterans with chronic combat-related PTSD (Battista et al., 2007). The RBANS is also routinely used in military medical centers for TBI assessments (Jaffee et al., 2009).

Quick Inventory of Depressive Symptomatology (QIDS)

The Quick Inventory of Depressive Symptomatology (QIDS) was administered at each session to assess symptoms of depression. The QIDS is a 16-item measure of

depressive symptom severity adapted from the 30-item Inventory of Depressive Symptomatology (IDS). The QIDS scoring system converts responses to the 16 items into measurements of the nine DSM-IV symptom criterion domains for major depression. These domains are 1) sad mood; 2) concentration; 3) self criticism; 4) suicidal ideation; 5) interest; 6) energy/fatigue; 7) sleep disturbance (initial, middle, and late insomnia or hypersomnia; 8) decrease/increase in appetite/weight; and 9) psychomotor agitation/retardation. Each symptom item is rated on a scale of 0 – 3 , with the higher score indicating greater symptom severity. The total score for the QIDS ranges from 0 – 27. Data analysis by Rush et al. (2003) demonstrated that the QIDS has highly acceptable psychometric properties with a high internal consistency of .86. The total score on the QIDS was also highly correlated with other measures of depression, including the Inventory of Depressive Symptomatology (IDS-SR_{30}; Rush et al., 1996; r = .96) the Hamilton Rating Scale for Depression (HAM-D_{24}; Hamilton 1960, 1967; Miller et al., 1985; r = .84;) (Rush et al., 1993).

Procedures

See Table 3 for an overview of the study procedures. Once participants completed the informed consent and agreed to take part in the study, they were interviewed by an assessment technician (either a doctoral level psychologist or a trained and supervised assessment technician). Study participants were reimbursed in the amount of $50.00 for the initial baseline assessment and $20.00 for each of the four follow up sessions. The total compensation amount for completing all five study sessions was $130.

At the baseline assessment session, demographic information was gathered and participants were administered a demographic questionnaire, Life Events Checklist

(LEC), Clinician Administered PTSD Scale (CAPS), PTSD Checklist (PCL), Quick Inventory of Depressive Symptomatology (QIDS), and the Repeatable Battery for the Assessment of Neuropsychological Status, form A, (RBANS-A). Because of safety concerns regarding the impact of the study medication on brain plasticity, we did not include anyone that had brain damage as defined by obtaining a Total Score on the RBANS-A that was two standard deviations or more below the average score.

The purpose of session one was to prepare the stimulus script and administer the study medication. The subject was first asked to provide a urine sample that was screened for illegal drugs that might affect the study methods. He was then orally administered either 15 mg of rapamycin or placebo, which appeared identical to rapamycin. All study personnel were blinded to the medication, which was prepared by a VA pharmacist. The subject was then asked to describe his most distressing combat experience (identified in the baseline assessment) by writing it on a standard script preparation form (see Appendix B). The study coordinator asked him to identify at least five physical responses, which were listed on the script preparation form, that he remembered experiencing during the described traumatic event. The study coordinator reviewed the written description and may have asked for clarification or elaboration. When the script preparation form was complete, the subject was administered the PCL and QIDS. Between sessions one and two, the study coordinator created an approximately 30-second script about the subject's worst combat experience, based on the information from the script preparation form. An example of a trauma script used in the study read as:

> It's 1990 and you're in Iraq. You're squad is minesweeping and doing everything by the book. Your friend that you have known all your life is on point. Your heart

> pounds and your palms are clammy. He goes into the field and takes three steps. Your stomach is in knots. You hear an explosion. Your body feels heavy as you clench your fist. Over half of your friend's body is gone. Your hands are trembling and your eyes are closed. You were his squad leader and now he's gone. You want to scream.

The combat experience was described in the second person, present tense and included a maximum of five physical responses that were chosen by the subject. The script was then recorded by a male study coordinator and saved as a .wav file to be used in session 2.

The participant returned one week later for session two, during which the script-driven memory reactivation procedure took place and physiological and subjective symptom measures were recorded. This session took place in a temperature- and sound-controlled laboratory at the Dallas VAMC's Clinical Research Unit. The subject was first asked to provide a urine sample to test for drugs that might affect psychophysiological measurements. He was then instructed to thoroughly wash his hands and forearms with Cetaphil soap to remove any substances on the skin that could prevent the electrodes from picking up the psychophysiological readings. The research coordinator then attached the recording electrodes, placed headphones over his ears, and asked the participant to remain in his chair and relax for 15 minutes. After the 15 minutes had passed, the subject listened to three recorded scripts over the headphones. The first script he heard was a standard, neutral script, followed by his personal combat trauma script, and then a second standard neutral script. Before the scripts were played, the electrodes recorded the subject's physiological baseline measurements. The physiological measures

that were recorded and assessed included heart rate, skin conductance, and electrical activity in the left lateral frontalis and the left corrugator muscle. The subject was instructed to carefully listen while each script was being played, and, after the script reading had ended, to imagine the experience described in the script as vividly and realistically as possible, as if he was re-experiencing it, until he heard a tone signal. The subject was then instructed to stop imagining the experience and to relax until he heard a second tone. The subject then rated, using 12-point Likert-type scales, the vividness of his imagery and his level of arousal, dominance, and emotions of sadness, anger, fear, disgust, surprise, happiness, and guilt during the imagery. A rest period followed, which lasted until the subject's heart rate had returned to a level that was within five percent of the heart rate level taken during the previous baseline, or a minimum of one minute. When the criteria for ending the rest period had been met, the laboratory computer prompted the technician to start the baseline period for the next script. After all three scripts had been completed, the subject completed a QIDS and PCL.

Participants returned for a follow-up session one month after session two. They were administered the CAPS, PCL, QIDS, and RBANS-B. Participants also returned three months after session 2 and were administered the CAPS, PCL, and QIDS.

For the current study, data gathered from the CAPS, RBANS, and QIDS during the baseline assessment and one-month follow-up will be analyzed (See Table 3).

Statistical Analyses

All data were entered using SPSS 16 for Windows™. CAPS, RBANS, and QIDS scores are calculated using ordinal scales, but are ordinal with assumption of standard intervals and are therefore considered to meet assumptions of parametric statistics.

Means, medians, and standard deviations will be calculated, when appropriate, for demographic variables (see Table 4). Means and standard deviations will also be calculated for the CAPS, RBANS, and QIDS (see Table 5).

Statistical analyses for each hypothesis are as followed:

Hypothesis I

In a sample of veterans with combat-related PTSD, participants who are treated with a single dose of rapamycin paired with traumatic memory reactivation will show a greater improvement in their cognitive performance, as measured by the RBANS at baseline and one-month follow-up, than participants who are treated with placebo paired with traumatic memory reactivation.

Hypothesis I was evaluated using a repeated-measures ANOVA, with type of intervention as the between groups factor and time as the repeated measure (baseline and one-month follow-up).

Hypothesis Ia

In a sample of veterans with combat-related PTSD, veterans from the OEF/OIF era who are treated with a single dose of rapamycin paired with traumatic memory reactivation will show a greater improvement in cognitive performance, as measured by the RBANS at baseline and one-month follow-up, than veterans from the Vietnam era who are treated with a single dose of rapamycin paired with traumatic memory reactivation.

Hypothesis Ia was evaluated using a repeated-measures ANOVA, with service era as the between groups factor and time as the repeated measure (baseline and one-month follow-up).

Hypothesis Ib

In a sample of veterans with combat-related PTSD, veterans from the OEF/OIF era who are treated with a single dose of rapamycin paired with traumatic memory reactivation will show a greater improvement in cognitive performance, as measured by the RBANS at baseline and one-month follow-up, than veterans from the OEF/OIF era who are treated with placebo paired with traumatic memory reactivation.

Hypothesis Ib was evaluated using a repeated-measures ANOVA, with type of intervention as the between groups factor and time as the repeated measure (baseline and one-month follow-up).

Hypothesis II

In the rapamycin-treated sample, a reduction in PTSD symptoms, as measured by the CAPS at baseline and one-month follow-up, will be associated with an improvement in cognitive performance, as measured by the RBANS at baseline and one-month follow-up. A decrease in CAPS scores from baseline to one-month follow-up will be associated with an increase in RBANS scores from baseline to one-month follow-up.

Hypothesis II was evaluated using correlation analysis with CAPS and RBANS change scores (One-month follow-up score – baseline score).

Hypothesis IIa

In the rapamycin-treated sample, the reduction in PTSD symptoms, as measured by the CAPS at baseline and one-month follow-up, will be greater in OEF/OIF veterans than in Vietnam veterans.

Hypothesis IIa was evaluated using a repeated-measures ANOVA, with service era as the between groups factor and time as the repeated measure (baseline and one - month follow-up).

Hypothesis III

In the rapamycin-treated sample, a reduction in depression severity, as measured by the QIDS at baseline and one-month follow-up, will be associated with an improvement in cognitive performance, as measured by the RBANS at baseline and one-month follow up. A decrease in QIDS scores from baseline to one-month follow-up will be associated with an increase in RBANS scores from baseline to one-month follow-up.

Hypothesis III was evaluated using correlation analysis with QIDS and RBANS change scores (one-month follow-up scores – baseline scores).

Hypothesis IIIa

In the rapamycin-treated sample, the reduction in depression symptoms, as measured by the QIDS at baseline and one-month follow-up, and improvement in cognitive performance, as measured by the RBANS at baseline and one- month follow-up, will be greater in OEF/OIF veterans than in Vietnam veterans.

Hypothesis IIIa was evaluated using a repeated-measures ANOVA, with service era as the between groups factor and time as the repeated measure (baseline and one-month follow-up).

CHAPTER FOUR

Results

Demographics

Two participants had missing data and two additional participants had questionable validity scores on the primary clinical outcome measure (CAPS). These four participants were excluded from the analyses and resulted in a total sample of 50 participants, of which 23 were randomly assigned to the control group and 27 to the rapamycin treatment group.

Table 4 lists demographic information for the two treatment groups and total sample. The mean age for subjects in the rapamycin group was 43.67 (SD=14.76) with a mean 14.07 years of education (SD=1.54). For subjects in the control group, the mean age was 42.22 years (SD=15.70) with a mean 13.61 years of education (SD=1.40). In the rapamycin group, 40.7% (n = 11) of the subjects were Caucasian, 29.6% (n = 8) were African-American, 22.2% (n = 6) were Hispanic, 3.7% (n = 1) were American Indian/Alaska Native, and 3.7% (n = 1) were other ethnicities. In the control group, 56.5% (n = 13) were Caucasian, 30.4% (n = 7) were African American, 4.3% (n = 1) were Hispanic, and 8.7% (n = 2) were other ethnicities. In regards to service era, 33.3% (n = 9) of participants in the rapamycin group were veterans from the Vietnam era, 22.2% (n = 6) were from the Gulf War era, and 44.4% (n = 12) were from the OEF/OIF era. In the placebo group, 34.8% (n = 8) of the subjects were veterans from the Vietnam era and 65.2% (n = 15) were from the OEF/OIF era.

Analyses of the demographic data found no significant differences between treatment groups with regard to age, ethnicity, education level, marital status,

employment status, or branch of service ($p > .05$ for all of these comparisons). There was a significant difference between treatment groups with regard to service era. One hundred percent (6 of 6) of veterans of Desert Storm/Bosnia/Somalia were randomized to the rapamycin treatment group compared to 47% (21 of 44) of others (Fisher's exact $p = .024$). Analyses of baseline measures of psychopathology (CAPS, QIDS) and cognitive performance (RBANS) revealed no significant differences between the placebo and rapamycin treatment groups ($p > .05$ for all of these comparisons).

Main Analyses

Hypothesis I

In a sample of veterans with combat related PTSD, veterans who are treated with a single dose of rapamycin paired with traumatic memory activation will show a greater improvement in their cognitive performance, as measured by the RBANS at baseline and one-month follow-up, than participants who are treated with placebo paired with traumatic memory activation.

A repeated measures ANOVA was conducted to assess the impact of two different interventions (rapamycin, placebo) on participants' scores on the RBANS, across two time periods (baseline, one-month follow-up). There was no significant interaction between treatment group and time; Wilks Lambda = 1.00, F (1, 48) = .001, p = .975, partial eta squared = .000. There was no significant main effect for time; Wilks Lambda = 1.00, F (1, 48) = .003, p = .955, partial eta squared = .000. The main effect comparing the two type of interventions revealed no significant differences in the effectiveness of the two interventions in the entire sample; F (1,48) = .01, p = .921, partial eta squared < .001.

Hypothesis Ia

In a sample of veterans with combat-related PTSD, veterans from the OEF/OIF era who are treated with a single dose of rapamycin paired with traumatic memory reactivation will show a greater improvement in cognitive performance, as measured by the RBANS at baseline and one-month follow-up, than veterans from the Vietnam era who are treated with a single dose of rapamycin paired with traumatic memory reactivation.

A repeated measures ANOVA was conducted to assess the impact of service era (Vietnam, OEF/OIF) on the RBANS scores of participants in the rapamycin treatment group, across two time periods (baseline, one-month follow-up). There was no significant interaction between service era type and time; Wilks Lambda = .96, F (1, 19) = .76, p = .395, partial eta squared = .038. There was no significant main effect for time; Wilks Lambda = 1.00, F (1, 19) = .05, p = .82, partial eta squared = .003. The main effect comparing the two service eras revealed no significant differences in the RBANS scores of the Vietnam era and OEF/OIF era participants in the rapamycin treatment group; F (1,19) = .02, p = .894, partial eta squared = .001.

Hypothesis Ib

In a sample of OEF/OIF veterans with combat-related PTSD, veterans treated with a single dose of rapamycin paired with traumatic memory reactivation will show a greater improvement in cognitive performance, as measured by the RBANS at baseline and one-month follow-up, than veterans who are treated with placebo paired with traumatic memory reactivation.

A repeated measures ANOVA was conducted to assess the impact of two different interventions (rapamycin, placebo) on the RBANS scores of participants from the OEF/OIF era, across two time periods (baseline and one-month follow-up). There was no significant interaction between treatment group and time; Wilks Lambda = .999, F (1, 25)= .03, p = .862, partial eta squared = .001. There was no significant main effect for time; Wilks Lambda = .993, F (1, 25) = .17, p = .685, partial eta squared = .007. The main effect comparing the two types of interventions was not significant revealed no significant difference between rapamycin and placebo in the RBANS scores for OEF/OIF veterans; F (1, 25) = .25, p = .618, partial eta squared = .010.

Hypothesis II

In the rapamycin-treated sample, a reduction in PTSD symptoms, as measured by the CAPS at baseline and one-month follow-up, will be associated with an improvement in cognitive performance, as measured by the RBANS at baseline and one-month follow-up. A decrease in CAPS scores from baseline to one-month will be associated with an increase in RBANS scores from baseline to one-month.

A two-tailed Pearson's correlation revealed a nonsignificant relationship between CAPS and RBANS change scores (r = .113, n = 27, p = .58).

Hypothesis IIa

In the rapamycin-treated sample, the reduction in PTSD symptoms, as measured by the CAPS at baseline and one-month follow-up, and improvement in cognitive performance, as measured by the RBANS at baseline and one-month follow-up, will be greater in OEF/OIF veterans than in Vietnam veterans.

A multivariate repeated measures ANOVA was conducted to test the impact of service era (Vietnam vs. OEF/OIF) on participants' scores on the CAPS and RBANS, across two time periods (baseline and one-month follow-up). There was no significant interaction between service era and time; Wilks Lambda = .899, F (2,18) = 1.01, p = .383, partial eta squared = .10. There was a significant main effect for time; Wilks Lambda = .71, F (2, 18) = 3.71, p = .045, partial eta squared = .29. The main effect in comparison of service era groups revealed no significant difference between Vietnam veterans and OEF/OIF veterans on the amount of reduction in PTSD symptoms (CAPS) and improvement in cognitive performance (RBANS); Wilks Lambda = .833, F (2, 18) = 1.80, p = .194, partial eta squared = .167. Univariate tests indicated that there was a significant effect for time on the CAPS, F (1, 19) = 7.66, p = .012, partial eta squared = .29, but not on the RBANS, F (1, 19) = .05, p = .821, partial eta squared = .003.

Hypothesis III

In the rapamycin-treated sample, a reduction in depression severity, as measured by the QIDS at baseline and one-month follow-up, will be associated with an improvement in cognitive performance, as measured by the RBANS at baseline and one-month follow up. A decrease in QIDS scores from baseline to one-month follow-up will be associated with an increase in RBANS scores from baseline to one-month follow-up.

A two-tailed Pearson's correlation revealed a nonsignificant relationship between QIDS and RBANS change scores (r = .349, n = 27, p = .074).

Hypothesis IIIa

In the rapamycin-treated sample, the reduction in depression symptoms, as measured by the QIDS at baseline and one-month follow-up, and improvement in

cognitive performance, as measured by the RBANS at baseline and 1- month follow-up, will be greater in OEF/OIF veterans than in Vietnam veterans.

A multivariate repeated measures ANOVA was conducted to the test the impact of service era (Vietnam vs. OEF/OIF) on participants' scores on the QIDS and RBANS, across two time periods (baseline and one-month follow-up). There was no significant interaction between service era and time; Wilks Lambda = 8.55, F (2, 18) = 1.52, p = .245, partial eta squared = .145. There was no significant main effect for time; Wilks Lambda = .79, F (2, 18) = 2.41, p = .118, partial eta squared = .211. The main effect comparing the two service era groups revealed no significant differences in either the QIDS or the RBANS scores between Vietnam and OEF/OIF veteran groups; Wilks Lambda = .813, F (2, 18) = 2.07, p = .155, partial eta squared = .19.

Exploratory Analyses

A repeated measures ANOVA was conducted to evaluate the impact of the two different treatment interventions (rapamycin and placebo) on RBANS total scores of veterans who demonstrated a clinically significant reduction (≥ 20 points) in their CAPS score from baseline to one-month follow-up. There was a significant interaction between time and treatment intervention; Wilks Lambda = .44, F (1, 13) = 16.74, p = .001, partial eta squared = .563. There was a significant main effect for time; Wilks Lambda = .64, F (1, 13) = 7.44, p = .017, partial eta squared = .364. There was not a significant main effect for treatment intervention; F (1,13) = .216, p = .650, partial eta squared = .016. Pairwise comparisons showed a significant improvement between baseline and one-month follow-up on the RBANS for participants in the placebo group, mean difference = 10.00, p = .002.

Repeated measures ANOVAs were conducted to evaluate the impact of the two different treatment interventions (rapamycin and placebo) on the RBANS subscale scores of veterans who demonstrated a clinically significant reduction (≥ 20 points) in their CAPS score from baseline to one-month follow-up. There was a significant interaction between time and treatment intervention for the RBANS immediate memory subscale; Wilks Lambda = .53, F (1, 13) = 11.65, p = .005, partial eta squared = .473. There was no significant main effect for time; Wilks Lambda = .95, F (1, 13) = .73, p = .408, partial eta squared = .053. There was no significant main effect for treatment intervention; (F (1, 13) = .15, p = .706, partial eta squared = .011. Pairwise comparisons showed a significant improvement between baseline and one-month follow-up on the immediate memory RBANS subscale for the placebo group (mean difference 13.50, p = .027) and a significant decline between baseline and one-month follow-up for the rapamycin group (mean difference -8.09, p = .028).

A repeated measure ANOVA for the RBANS language subscale revealed a significant main effect for time; Wilks Lambda = .49, F (1, 13) = 13.77, p = .003, partial eta squared = .514. There was no significant main effect for treatment intervention; F (1, 13) = .17, p = .684, partial eta squared = .013. There was no significant interaction between time and treatment intervention for the RBANS language subscale; Wilks Lambda = .973, F (1, 13) = 13.77, p = .555, partial eta squared = .03. Pairwise comparisons showed a significant improvement between baseline and one-month follow-up on the RBANS language subscale for the placebo group (mean difference 11.25, p = .026) and a significant improvement between baseline and one-month follow-up for the rapamycin group (mean difference 8.09, p = .010).

Results of repeated measures ANOVAs revealed no significant main effects or interactions on the RBANS subscales for visuospatial /constructional abilities, attention, and delayed memory.

CHAPTER FIVE

Discussion

The primary objective of the current study was to determine if, in a sample of male veterans with combat-related PTSD, participants treated with a single dose of rapamycin paired with traumatic memory reactivation would show an improvement in cognitive performance, as measured by the RBANS at baseline and one-month follow-up, relative to veterans receiving placebo paired with traumatic memory activation. Results revealed no significant differences between treatment groups on the RBANS. This finding remained the same regardless of whether the index trauma occurred more recently (OEF/OIF veterans) or decades ago (Vietnam veterans). There was a significant difference between the one-month follow-up RBANS scores when the sample was limited to participants who showed a clinically significant reduction (≥ 20 points) in their CAPS score. The scores of participants in the rapamycin group showed little change while participants in the control group showed a modest improvement in their RBANS scores.

The results demonstrating a lack of improvement in cognitive performance, when there was a reduction in PTSD symptoms lie in contrast to most of the previous studies investigating the relationship between cognitive performance and PTSD symptoms. Differences between previous research and the current study may explain these inconsistencies. One of the most significant differences between previous and the current study is the type of treatment medications utilized and their different mechanisms of action and associated therapeutic effects. The medications utilized in previous studies include paroxetine, memantine, D-cycloserine, and phenytoin. Selective serotonin

reuptake inhibitors (SSRIs), such as paroxetine, have been shown to foster neurogenesis in the hippocampus and reverse hippocampal atrophy (Duman, Nakagawa, & Malberg. 2001; Malberg, Eisch, Nestler, & Duman, 2000). In fact, a recent study using escitalopram, another SSRI, to treat stroke survivors resulted in an overall improvement in cognitive functioning that was independent of the medication's effect on depression (Jorge et al., 2010). These findings suggest that the cognitive improvement associated with SSRI use is not simply the result of a reduction in psychological distress. Memantine, a non-competitive NMDA antagonist, and D-cycloserine, a partial NMDA agonist, have been shown to improve memory deficits in individuals with Alzheimer's disease and vascular dementia (Ferris, 2003; Jones, Wesnes, & Kirby, 1991; Schwartz, Hashtroudi, Herting, Schwartz, & Deutsch, 1996; Tariot et al., 2004; Wilcox, Mobius, & Stoffler, 2002). NMDA is a receptor of glutamate and both are involved in mechanisms underlying learning and memory (Riedel, Platt, & Micheau, 2003). Glutamate dysfunction has been linked PTSD, as well as mood disorders and schizophrenia (Coyle, J. T., 2006; Reul & Nutt, 2008; Sanacora, Zarate, Krystal, & Manji, 2008). In summary, the medications used in previous studies appear to have mechanisms of action that lead to improvements in cognitive performance independent of psychological symptom improvement. Although the full impact of rapamycin treatment neurological structure and function is not fully understood, it does not appear, at this point, to have a similar action.

Length of treatment is another factor that distinguishes the current study from previous research and may explain the lack of improvement in cognitive performance. All of the previous studies utilized longer periods of treatment, ranging from four weeks to nine months. It is possible that if participants in the current study were given a higher

dose of rapamycin and/or took part in repeated treatment sessions of rapamycin paired with traumatic memory reactivation, an improvement in cognitive performance might have been seen due to a greater reduction in PTSD symptoms. However, the participants in the current study who received rapamycin and experienced a 20-points or greater reduction in their CAPS scores did not show improvement in cognitive performance.

Another difference between previous studies and the current investigation was the time between the baseline assessment of cognitive performance and the follow-up assessment. In the current study, there was a five-week time lapse between the two assessments. In other studies, this time period ranged from eight weeks to nine months (three months was the most common time period between baseline assessment and follow-up). It is possible that the biological and psychological processes that result in improved cognitive performance take a longer period of time to occur. For example, a previous study utilizing phenytoin to treat PTSD found a 6% increase in whole brain volume and significant correlations between an increase in hippocampal volume and a reduction in PTSD symptoms and improvement in executive functioning (Bremner et al., 2005). This points to structural changes in the brain that might take a longer period of time to develop adequately enough to be reflected in neuropsychological testing. In contrast, another study, by the same research group, investigating the use paroxetine to treat PTSD found no correlation between change in memory performance and change in hippocampal volume, despite a significant improvement in PTSD symptoms. To help elucidate the effect of rapamycin with traumatic memory reactivation on the brain, future studies might utilize neuroimaging to help determine if there are any structural or functional changes resulting from treatment.

Another factor that might explain the lack of significant findings for improved cognitive performance was the restricted range of RBANS scores. Potential study participants were screened for significant cognitive impairments at the baseline assessment with the RBANS. Individuals with a Total Score that was two standard deviations or more below the average were excluded from participation in the study as a precaution due to concerns about rapamycin's effect on synaptic plasticity. As a result, this sample of veterans did not appear to be experiencing significant difficulty with cognitive performance. This can be seen in the fairly average baseline RBANS scores of the veterans in the rapamycin group (mean score=92.1, SD=13.7) and placebo group (mean score = 91.7, SD=12.5). According to the scoring rules of the RBANS, a mean standard score of 100 is Average, with a standard deviation 15. In contrast to the present study, a previous study by Battista et al. (2007) that studied the effects of memantine on psychiatric and cognitive symptoms of PTSD limited participation to veterans who scored one standard deviation or more below the average on the attention and delayed memory subtests of the RBANS. Although this study's sample size was extremely small (n=4), a significant improvement was found on delayed memory. In the subgroup analyses of participants from the rapamycin and placebo groups that experienced a significant reduction (≥ 20 points) in their CAPS score from baseline to one-month follow-up, the placebo group, which showed a ten point improvement in RBANS scores, had a baseline mean RBANS score (83.5) that was more than one standard deviation below average, while the rapamycin, which did not show an improvement, had a baseline mean RBANS score (87) that was less than one standard deviation below average. Although the difference between the RBANS mean baseline scores of the two groups was

3.5 points, it is likely that PTSD symptom improvement would lead to a significant improvement in cognitive performance only if there was a significant impairment to begin with.

Another possible explanation for the significant difference on the one-month follow-up RBANS scores between the rapamycin group and control groups with a clinically significant reduction in PTSD symptoms might lie in the psychiatric history of the two groups. Compared to the placebo group, the rapamycin group had a higher percentage of participants with a history of depression and/or substance abuse or dependence, although no significant difference between the groups was found with regard to history of depression, alcohol abuse or dependence, or drug abuse or dependence ($p >$ .05 for all of these comparisons). In the rapamycin subgroup that experienced a clinically significant reduction in PTSD symptoms, 72% of participants had a history of depression, 72% had a history of alcohol abuse or dependence, and 27% had a history of drug abuse or dependence. In the placebo group that experienced a clinically significant reduction in PTSD symptoms, 25% of participants had a history of depression and 25% had a history of alcohol abuse or dependence. It is possible that a history of depression or substance abuse or dependence leads to lasting changes in the brain affecting cognitive performance that are not improved by a reduction in PTSD symptoms.

Although an improvement in cognitive performance was not found, the fact that rapamycin treatment did not result in a decline in cognitive performance is important. Evidence of a decline in cognitive functioning following treatment for a disorder already associated with cognitive impairment would be problematic. Rapamycin has shown promise as a novel treatment for PTSD and the lack of evidence for a decline in cognitive

functioning following treatment allows for further investigations that utilize more treatment sessions of rapamycin paired with traumatic memory activation and higher doses of rapamycin.

Limitations

Limitations of this study include the relatively small size of the study. It is possible that significant between group differences on the RBANS would have been revealed if a larger sample size had been studied. In addition, the sample was limited to male combat veterans who utilize the Veteran's Administration for PTSD treatment and may not be representative of veterans in general. Veterans with PTSD due to combat-related trauma may also not be representative of individuals with PTSD related to other traumas. The exclusion of women from the study minimizes the ability to generalize the findings to non-male populations. Another limitation of this study was the single administration of rapamycin paired with traumatic memory reactivation. It is possible that multiple treatment sessions would have resulted in greater PTSD symptom reduction and an observable improvement in cognitive performance.

Conclusion

In summary, the results suggest that a single 15 mg dose of rapamycin paired with traumatic memory reactivation does not have either a positive or negative impact on cognitive performance. This treatment combination did not result in a significant improvement in cognitive performance, even when there was a reduction in PTSD symptom severity. Research demonstrating that rapamycin paired with traumatic memory reactivation results in a reduction of PTSD symptoms will likely lead to future studies that utilize multiple sessions of rapamycin paired with traumatic memory reactivation.

Future research studies should continue to assess cognitive performance to determine if an increase in treatment sessions will lead to any change in cognitive impairment. Rapamycin is a promising medication that deserves continued study to determine its place in PTSD treatment.

REFERENCES

Alexander, M. P. (1995). Mild traumatic brain injury: Pathophysiology, natural history, and clinical management. *Neurology, 45*, 1253 – 1260.

American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington, DC: Author.

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., rev.). Washington, DC: Author.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., rev.). Washington, DC: Author.

Archibald, H. C. & Tuddenham, R. D. (1965). Resistant stress reaction after combat: A 20-year follow-up. *Archives of General Psychiatry, 12*, 475 – 481.

Bailey, C. H., Bartsch, D., & Kandel, E. R. (1996). Towards a molecular definition of long-term memory storage. *Proceedings of the National Academy of Sciences USA, 93*, 13445 – 13452.

Barrett, D. H., Green, M. L., Morris, R., Giles, W. H., & Croft, J. B. (1996). Cogntive functioning and posttraumatic stress disorder. *American Journal of Psychiatry, 153*(11), 1492 – 1494.

Battista, M. A., Hierholzer, R., Khousam, H. R., Barlow, A., & O'Toole, S. (2007). Pilot trial of memantine in the treatment of posttraumatic stress disorder. *Psychiatry, 70*(2), 167 – 174.

Beaumont, V., Zhong, N., Fletcher, R., Froemke, R. C., & Zucker, R. S. (2001). Phosphorylation and local presynaptic protein synthesis in calcium- and calcinuerin-dependent induction of crayfish long term facilitation. *Neuron, 32*, 489 – 501.

Bleich, A., & Solomon, Z. (2004). Evaluation of psychiatric disability in PTSD of military origin. *The Israel Journal of Psychiatry and Related Sciences, 41,* 268 – 276.

Blundell, J., Kouser, M., & Powell, C. M. (2008). Systemic inhibition of mammalian target of rapamycin inhibits fear memory reconsolidation. *Neurobiology of Learning and Memory, 90*(1), 28-35.

Bouton, M. E. (1993). Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. *Psychological Bulletin, 114*, 80 – 99.

Brandes, D., Ben-Sachar, G., Gilboa, A., Bonne, O., Freedman, S., & Shalev, A. Y. (2002). PTSD symptoms and cognitive performance in recent trauma survivors. *Psychiatry Research, 110*, 231 – 238.

Bremner, J. D. (2007). Neurobiology of posttraumatic stress disorder. In G. Fink (Ed.), *Encyclopedia of Stress* (2nd ed.) (pp.152 - 157). San Diego, CA: Academic Press.

Bremner, J. D., Mletzko, T., Welter, S., Quinn, S., Williams, C., Brummer, M., . . . Nemeroff, C. B. (2005). Effects of phenytoin on memory, cognition and brain structure in post-traumatic stress disorder: A pilot study. *Journal of Psychopharmacology, 19*(2), 159 - 165.

Bremner, J. D., Randall, P., Scott, T. M., Bronen, R. A., Seibyl, J. P., Southwick, S. M., . . . Innis, R. B. (1995). MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *American Journal of Psychiatry, 152,* 973 – 981.

Bremner, J. D., Randall, P., Scott, T. M., Capelli, S. Delaney, R., McCarthy, G., Charney, D. S. (1995). Deficits in short-term memory in adult survivors of childhood abuse. *Psychiatric Research, 59*, 97 – 107.

Bremner, J. D., Scott, T. M., Delaney, R. C., Southwick, S. M., Mason, J. W., Johnson, D. R., . . . Charney, D. S. (1993). Deficits in short-term memory in posttraumatic stress disorder. *The American Journal of Psychiatry, 150*, 1015 – 1019.

Bremner, J. D., Southwick, S. M., Darnell, A., & Charney, D. S. (1996). Chronic PTSD in Vietnam veterans: Course of illness and substance abuse. *American Journal of Psychiatry, 153*(3), 369 - 375.

Breslau, N. (2001). Outcomes of posttraumatic stress disorder. *Journal of Clinical Psychiatry, 62*(Suppl. 17*)*, 55 – 59.

Breslau, N. (2002). Epidemiologic studies of trauma, posttraumatic stress disorder, ad other psychiatric disorders. *Canadian Journal of Psychiatry, 47*, 923 – 929.

Breslau, N., Chase, G. A., & Anthony, J. C. (2002). The uniqueness of the DSM definition of post-traumatic stress disorder: Implications for research. *Psychological Medicine, 32*, 573 – 576. doi: 10.1017/S0033291701004998

Breslau, N., Davis, G. C., Peterson, E. L., & Schultz, L. (1997). Psychiatric sequelae of posttraumatic stress disorder in women. *Archives of General Psychiatry, 54*(1), 81 – 87.

Breslau, N., Davis, G. C., Peterson, E. L. & Schultz, L. R. (2000). A second look at Comorbidity in victims of trauma: The posttraumatic stress disorder – major depression connection. *Biological Psychiatry, 48*, 902 – 909

Breslau, N., Davis, G. C., & Schulz, L. R. (2003). Posttraumatic stress disorder and the incidence of nicotine, alcohol, and other drug disorders in persons who have experienced trauma. *Archives of General Psychiatry, 60*, 289 – 294.

Bryant, R. A. (2008). Disentangling mild traumatic brain injury and stress reactions. *New England Journal of Medicine, 385*(5), 525 – 527.

Burnett, P. E., Barrow, R. K., Cohen, N. A., Snyder, S. H., & Sabatini, D. M. (1998). RAFT1 phosphorylization of the translational regulators p70 S6 kinase and 4E-BP1. *Proceedings of the National Academy of Sciences USA, 95*, 1432 – 1437.

Burriss, L., Ayers, E., Ginsberg, J., & Powell, D. A. (2008). Learning and memory impairment in PTSD: Relationship to depression. *Depression and Anxiety, 25*, 149 – 157. doi: 10.1002/da.20291

Burstein, A. (1984). Treatment of post-traumatic stress disorder with imipramine. *Psychosomatics, 25*, 683 – 687.

Burstein, A. (1985). Post-traumatic flashbacks, dream disturbance, and mental imagery. *Journal of Clinical Psychiatry, 46*, 374 – 378.

Bustamante, V., Mellman, T. A., David, D., & Fins, A. I. (2001). Cognitive functioning and the early development of PTSD. *Journal of Traumatic Stress, 14*(4), 791 – 797. doi: 10.1023/A:1013050423901

Cai, W., Blundell, J., han, J., Greene, R., & Powell, C. M. (2006). Postreactivation glucocorticoids impair recall of established fear memory. *The Journal of Neuroscience, 26*(37), 9560 – 9566. Doi: 10.1523/JNEUROSCI.2397-06.2006

Casadio, A., Martin, K. C., Glustetto, M., Zhu, M. C., Bartsch, D., Bailey, C. H., & Kandel, E. R. (1999). A transient, neuron-wide form of CREB-mediated long-term facilitation can be stabilized at specific synapses by local protein synthesis. *Cell, 99*, 221 – 237.

Chen, Y. W., Smith, M. L., Sheets, M., Ballaron, S., Trevillyan, J. M., Burke, S. E., . . . Djuric, S. W. (2007). Zotarolimus, a novel sirolimus analogue with potent anti-proliferative activity on coronary smooth muscle cells and reduced potential for systemic immunosuppression. *Journal of Cardiovascular Pharmacology, 49*, 228 – 235.

Chilcoat, H. D., & Breslau, N. (1998a). Investigations of the causal pathways between PTSD and drug use disorders. *Addictive Behaviors, 23*(6), 827 – 840. doi: 10.1016/S0306-4603(98)00069-0

Chilcoat, H. D., & Breslau, N. (1998b). Posttraumatic stress disorder and drug disorders: Testing causal pathways. *Archives of General Psychiatry, 55*, 913 – 917.

Cooper, D. B., Mercado-Couch, J. M., Critchfield, E., Kennedy, J., Vanderploeg, R. D., DeVillibis, C., & Gaylord, K. M. (2010). Factors influencing cognitive functioning following mild traumatic brain injury in OIF/OEF burn patients. *NeuroRehabilitation, 26*(3), 233 – 238.

Coyle, J. T. (2006). Glutamate and schizophrenia: Beyond the dopamine hypothesis. *Cellular and Molecular Neurobiology, 4 – 6*, 365 – 384.

Danckwerts, A., & Leathem, J. (2003). Questioning the link between PTSD and cognitive dysfunction. *Neuropsychology Review, 13*(4), 221 – 235.

Dann, S. G., Selvaraj, A., & Thomas, G. (2007). mTOR complex 1-S6K1 signaling: At the crossroads of obesity, diabetes, and cancer. *Trends in Molecular Medicine, 13*, 252 – 259.

Davis, H. P., & Squire, L. R. (1984). Protein synthesis and memory: A review. *Psychological Bulletin, 96*(3), 518 – 559.

Deering, C. G., Glover, G. G., Ready, D., Eddleman, H. C., & Alarcon, R. D. (1996). Unique patterns of comorbidity in posttraumatic stress disorder from different sources of trauma. *Comprehensive Psychiatry, 37*(5), 336 – 346.

Dickie, E. W., Brunet, A., Akerib, V. Armony, J. L. (2008). An fMRI investigation of memory encoding in PTSD: Influence of symptom severity. *Neuropsychologia, 46*, 1522 – 1531.

Dudai, Y. (2004). The neurobiology of consolidations, or, how stable is the engram? *Annual Review of Psychology, 55*, 51 – 86. doi: 10.1146/annurev.psych.55.090902.142050

Duman, R. S., Nakagawa, S., Malberg, J. (2001). Regulation of adult neurogenesis by antidepressant treatment. *Neuropsychopharmacology, 25*, 836 – 844.vbg

Duvarci, S., & Nader, K. (2004). Characterization of fear memory reconsolidation. *The Journal of Neuroscience, 24*(42), 9269 – 9275. Doi: 10.1523/jneurosci.2971-04.2004

Ferris, S. H. (2003). Evaluation of memantine for the treatment of Alzheimer's disease. *Expert Opinion in Psychopharmacotherapy, 4*(12), 2305 – 2313.

French, L. M., & Parkinson, G. W. (2008). Assessing and treating veterans with traumatic brain injury. *Journal of Clinical Psychology, 64*(8), 1004 – 1013. doi: 10.1002/jclp.20514

Geuze, E., Vermetten, E., de Kloet, C. S., Hijman, R., & Westenberg, H. G. M. (2009). Neuropsychological performance is related to current social and occupational functioning in veterans with posttraumatic stress disorder. *Depression and Anxiety, 26,* 7 – 15.

Gil, T., Calev, A., Greenberg, D., Kugelmass, S., & Lerer, B. (1990). Cognitive functioning in post-traumatic stress disorder. *Journal of Traumatic Stress, 3*, 29 – 45.

Gilbertson, M. A., Paulus, L. A., Williston, S. K., Gurvits, T. V., Lasko, N. B., Pitman, R. K., & Orr, S. P. (2006). Neurocognitive function in monozygotic twins discordant for combat exposure: Relationship to posttraumatic stress disorder. *Journal of Abnormal Psychology, 115*(3), 484 – 495. doi: 10.1037/0021-843X.115.3.484

Golier, J. & Yehuda, R. (1997). Sustained attention in combat-related posttraumatic stress disorder. *Integrative Physiological and Behavioral Science, 32*(1), 52 – 61.

Green, M. F., Kern, R. S., Braff, D. L., & Mintz, J. (2000). Neurocognitive deficits and functional outcomes in schizophrenia: Are we measuring the “right stuff”? *Schizophrenia Bulletin, 26*, 119 – 136.

Gueze, E., Vermetten, E., de Kloet, C. S., Hijman, R., Westernber, H. G. M. (2009). Neuropsychological performance is related to current social and occupational

functioning in veterans with posttraumatic stress disorder. *Depression and Anxiety, 26*, 7 – 15, doi: 10.1002/da.20476

Gurvits, T. V., Lasko, N. B., Schacter, S. C., Kuhne, A. A., Orr, S. P., & Pitman, R. K. (1993). Neurological status of Vietnam veterans with chronic posttraumatic stress disorder. *Journal of Neuropsychiatry and Clinical Neurosciences, 5*, 183 – 188.

Hamilton, M. (1960). A Rating Scale for Depression. *Journal of Neurology, Neurosurgery, and Psychiatry, 23*, 56 – 62.

Hamilton, M. (1967). Development of a rating scale for primary depressive illness.. *The British Journal of Social and Clinical Psychology, 6*, 278 – 296.

Hart, J., Jr., Kimbrell, T., Fauver, P., Cherry, B. J., Pitcock, J., Booe, L. Q., . . . Freeman, T. W. (2008). Cognitive dysfunctions associated with PTSD: Evidence from World War II prisoners of war. *The Journal of Neuropsychiatry and Clinical Neurosciences, 20*, 309 – 316.

Hay, N., & Sonenberg, N. (2004). Upstream and downstream of mTOR. *Genes and Development, 18, 1926 - 1945.*

Heresco-Levy, U., Kremer, I., Javitt, D. C., Goichman, R., Reshef, A., Blanaru, M., & Cohen, T. (2002). Pilot-controlled trial of D-cycloserine for the treatment of post-traumatic stress disorder. *International Journal of Neuropsychopharmacology, 5*, 301 – 307.

Hoeffer, C. A. & Klann, E. (2009). Mtor signaling: At the crossroads of plasticity, memory, and disease. *Trends in Neuroscience, 33*(2), 67 – 75. doi: 10.1016/j.tins.2009.11.003

Hoge, C. W., McGurk, D., Thomas, J. L., Cox, A. L., Engel, C. C., & Castro, C. A. (2008). Mild traumatic brain injury in U.S. soldiers returning from Iraq. *The New England Journal of Medicine, 358*(5), 453 – 463.

Horner, M. D., & Hamner, M. B. (2002). Neurocognitive functioning in posttraumatic stress disorder. *Neuropsychology Review, 12*, 15 – 30. doi: 10.1037/0894

Institute of Medicine of the National Academies, Board on Population Health and Public Health Practice, Committee of Gulf War and Health: Brain Injury in Veterans and Long-Term Health Outcomes. (2008). *Gulf war and health: Volume 7: Long-term consequences of traumatic brain injury.* Washington, DC: The National Academies Press.

Iverson, G. L., Langlois, J. A., McCrea, M. A., & Kelly, J. P. (2009). Challenges associated with post-deployment screening for mild traumatic brain injury in military personnel. *The Clinical Neuropsychologist, 23*(8), 1299 – 1314.

Jaffee, M. S., Helmick, K. M., Girard, P. D., Meyer, K. S., Dinegar, K. & George, K. (2009). Acute clinical care and care coordination for traumatic brain injury within Department of Defense. *Journal of Rehabilitation Research & Development, 46*(6), 655 – 666. doi: 10.1682/JRRD.2008.09.0114

Jelinek, L., Jabobsen, D., Kellner, M., Larbig, F., Biesold, K. H., Barre, K., & Moritz, S. (2006). Verbal and nonverbal memory functioning in posttraumatic stress disorder (PTSD). *Journal of Clinical and Experimental Neuropsychology, 28*, 940 – 948. doi: 10.1080/13803390591004347

Jenkins, M. A., Langlais, P. J., Delis, D., & Cohen, R. A. (1998). Learning and memory in rape victims with posttraumatic stress disorder. *American Journal of Psychiatry, 155*, 278 – 279.

Jenkins, M. A., Langlais, P. J., Delis, D., & Cohen, R. A. (2000). Attentional dysfunction associated with posttraumatic stress disorder among rape survivors. *The Clinical Neuropsychologist, 14*, 7 – 12.

Johnsen, G., & Asbornsen, A. E. (2008). Consistent impaired verbal memory in PTSD: A meta-analysis. *Journal of Affective Disorders, 111*, 74 – 82. doi: 10.1016/j.jad.2008.02.007

Jones, R. W., Wesnes, K. A., & Kirby, J. (1991). Effects of NMDA modulation in scopolamine dementia. *Annals of the New York Academy of Science, 640*, 241 – 244.

Jordan, B. K., Marmar, C. R., Fairbank, J. A., Schlenger, W. E., Kulka, R. A., Hough, R. L., & Weiss, D. S. (1992). Problems in families of male Vietnam veterans with posttraumtic stress disorder. *Journal of Consulting and Clinical Psychology, 60*, 916-926.

Jorge, R. E., Acion, L., Moser, D., Adams, H. P., Jr., & Robinson, R. G. (2010). Escitalopram and enhancement of cognitive recovery following stroke. *Archives of General Psychiatry, 67*(2), 187 – 196.

Kalechstein, A. D., Newton, T. F., & van Gorp, W. G. (2003). Neurocognitive functioning is associated with employment status: A quantitative review. *Journal of Clinical and Experimental Neuropsychology, 25*, 1186 – 1191.

Keane, T. M., Caddell, J. M., & Taylor, K. L. (1988). Mississippi scale for combat-

related post-traumatic stress disorder: Three studies in reliability and validity. *Journal of Consulting and Clinical Psychology, 56,* 85-90.

Keane, T. M., & Kaloupek, D. G. (1997). Comorbid psychiatric disorders in PTSD. *Annals of the New York Academy of Sciences, 821*, 24 – 34.

Keane, T. M., Malloy, P. F., & Fairbank, J. A. (1984). Empirical development of an MMPI subscale for the assessment of combat-related post-traumatic stress disorder. *Journal of Consulting and Clinical Psychology, 52*, 888 – 891.

Kessler, R. C. (2000). Posttraumatic stress disorder: The burden to the individual and to society. *Journal of Clinical Psychiatry, 61*(suppl. 5), 5 – 12.

Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M., Nelson, C. B. (1995). Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of General Psychiatry, 52,*1048–60.

Koenen, K. C., Driver, K. L., Oscar-Berman, M., Wolfe, J., Folsom, S. Huang, M. T., & Schlesinger, L. (2001). Measures of prefrontal system dysfunction in posttraumatic stress disorder. *Brain and Cognition, 45*, 64 – 78.

Konorski, J. (1967). *Integrative Activity of the Brain*. Chicago: University of Chicago Press.

Kuhn, E., Blanchard, E. B., & Hickling, E. J. (2003). Posttraumatic stress disorder and psychosocial functioning within two samples of MVA survivors. *Behaviour Research and Therapy, 41*, 1105 – 1112.

Kulka, R. A., Schlenger, W. E., Fairbank, J. A., Hough, R. L., Jordan, B. K., Marmar, C. R., & Weiss, D. S. (1990). *Trauma and the Vietnam War generation: Report of*

findings from the National Vietnam Veterans Readjustment Study. New York: Brunner/Mazel.

LaGarde, G., Doyon, J. & Brunet, A. (2010). Memory and executive dysfunctions associated with acute posttraumatic stress disorder.*Psychiatry Research, 177*, 144 – 149. Doi: 10.1016/j.psychres.2009.02.002

Lupien, S. J., Maheu, F. S. (2007). Memory and stress. In G. Fink (Ed.), *Encyclopedia of Stress* (2nd ed., Vol.2, pp. 693-699). Amsterdam: Academic Press.

McCrea, M., Barr, W. B., Guskiewicz, K., Randolph, C., Marshall, S. W., Cantu, R., . . . Kelly, J. P. (2005). Standard regression-based methods for measuring recovery after sports-related concussion. *Journal of the International Neuropsychological Society, 11*(1), 58 – 69.

McCrea, M., Pliskin, N., Barth, J., Cox, D., Fink, J., French, L., . . . Yoash-Gantz, R. (2008). Official position of the military TBI task force on the role of neuropsychology and rehabilitation psychology in the evaluation, management, and research of military veterans with traumatic brain injury. *The Clinical Neuropsychologist, 22*(1), 10 – 26. doi: 10.1080/13854040701760981

McKay, C., Casey, J., Wertheimer, J., & Fichtenberg, N. (2007). Reliability and validity of the RBANS in a traumatic brain injured sample. *Archives of Clinical Neuropsychology, 21*, 91 – 98.

McKay, C., Wertheimer, J. C., Fichtenberg, N. L., & Casey, J. E. (2008). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Clinical utility in a traumatic brain injury sample. *The Clinical Neuropsychologist, 22*, 228 – 241. doi: 10.1080/13854040701260370

McNally, R. J. (2006). Cognitive abnormalities in post-traumatic stress disorder. *Trends in Cognitive Sciences, 10*(6), 271 – 277. doi: 10.1016/j.tics.2006.04.007

Magruder, K. M., Frueh, B. C., Knapp, R. G., Davis, L., Hammer, M. B., & Martin, R. H., . . . Arana, G. W. (2005). Prevalence of posttraumatic stress disorder in Veterans Affairs primary care clinics. *General Hospital Psychiatry, 27*, 169 – 179.

Malberg, J. E., Eisch, A. J., Nestler, E. J., & Duman, R. S. (2000). Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *Journal of Neuroscience, 20*, 9104 – 9110.

Martin, S. J., Grimwood, P. D., & Morris, R. G. M. (2000). Synaptic plasticity and memory: An evaluation of the hypothesis. *Annual Review of Neuroscience, 23*, 649 – 711.

Marvel, C. L., & Paradiso, S. (2004). Cognitive and neurological impairment in mood disorders. *Psychiatric Clinics of North America, 27*, 19 – 36.

Miller, I. W., Bishop, S., Norman, W. H., & Maddever, H. (1985). The modified Hamilton rating scale for depression: Reliability and validity. *Psychiatry Research, 14*, 131 – 142.

Monfils, M. H., Cowansage, K. K., Klann, E., LeDoux, J. E. (2009). Extinction-reconsolidation boundaries: Key to persistent attenuation of fear memories. *Science, 324*, 951 – 955.

Nader, K., Schafe, G. E., & Le Doux, J. E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature, 406*, 722 – 726.

North, C. S., Hong, B. A., Suris, A. M., & Spitznagel, E. L. (2008). Distinguishing distress and psychopathology among survivors of the Oakland/Berkeley firestorm. *Psychiatry, 71*(1), 35 – 45. doi: 10.1521/psych.2008.71.1.35

North, C. S., Kawasaki, A., Spitznagel, E. L., Hong, B. A. (2004). The course of PTSD, major depression, substance abuse, and somatization after a natural disaster. *Journal of Nervous & Mental Disease, 192*(12), 823 – 829.

North, C. S., Suris, A. M., & Adewuyi, S. (2010). Psychiatric comorbidities. In D. M. Benedek & G. H. Wynn (Eds.), *Clinical Manual for the Management of PTSD* (pp.101 – 127). Arlington, Virginia: American Psychiatric Publishing, Inc.

North, C. S., Smith, E. M., & Spitznagel, E. L. (1994). Posttraumatic stress disorder in survivors of a mass shooting. *American Journal of Psychiatry, 151*, 82 – 88.

North, C. S., Suris, A. M., Davis, M., & Smith, R. P. (2009). Toward validation of the diagnosis of posttraumatic stress disorder. *The American Journal of Psychiatry, 166*(1), 34 – 41.

North, C. S., Nixon, S. J., Shariat, S., Mallonee, S., McMillen, J. C., Spitznagel, E. L., & Smith, E. M. (1999). Psychiatric disorders among survivors of the Oklahoma City bombing. *JAMA, 282*(8), 755 – 762. doi: 10.1001/jama.282.8.755

Parsons, R.G., Gafford, G. M., Helmstetter, F. J. (2006). Translational control via the mammalian target of rapamycin pathway is critical for the formation and stability of long-term fear memory in amygdale neurons. *Journal of Neuroscience, 26*, 12977 - 12983.

Polusny, M. A., Kehle, S. M., Nelson, N. W., Erbes, C. R., Arbisi, P. A., & Thuras, P. (2011). Longitudinal effects of mild traumatic brain injury and posttraumatic

stress comorbidity on postdeployment outcomes in National Guard soldiers deployed to Iraq. *Archives of General Psychiatry, 68*(1), 79 – 89.

Przybyslawski, J., & Sara, S. J. (1997). Reconsolidation of memory after its reactivation. *Behavioural Brain Research, 84*(1-2), 241-246.

Raught, B., Gingras, A., & Sonenberg, N. (2001). The target of rapamycin (TOR) proteins. *Proceedings of the National Academy of Sciences USA, 98*, 7037 – 7044.

Randolph, C. (1998). *RBANS manual – Repeatable battery for the assessment of neuropsychological status.* San Antonio, TX: The Psychological Corporation.

Reul, J. M. H. M., & Nutt, D. J. (2008). Glutamate and cortisol – A critical confluence in PTSD? *Journal of Psychopharmacology, 22*(5), 496 – 472.

Rush, A. J., Gillion, C. M., Basco, M. R., Jarrett, R. B., Trivedi, M. H. (1996). The inventory of depressive symptomatology (IDS): Psychometric properties. *Psychological Medicine, 26*(3), 477 – 486.

Sachinvala, N., von Scotti, H., McGuire, M., Fairbanks, L., Bakst, K., McGuire, M., & Brown, N. (2000). Memory, attention, function, and mood among patients with chronic posttraumatic stress disorder. *Journal of Nervous and Mental Disease, 188*, 818 – 823.

Samuelson, K. W., Metzler, T. J., Rothlind, J., Choucroun, G., Neylan, T. C., Lenoci, M., . . . Marmar, C. R. (2006). Neuropsychological findings in posttraumatic stress disorder and alcohol abuse. *Neuropsychology, 20*(6), 716 – 726. doi: 10.1037/0894-4105.20.6.716

Sanacora, G., Zarate, Jr., C. A., Krystal, J., & Manji, H. K. (2008). Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nature Reviews Drug Discovery, 7*, 426 – 437.

Sara. S. J. (2000). Retrieval and reconsolidation: Toward a neurobiology of remembering. *Learning and Memory, 7*, 73 - 84.

Schnurr, P. P., Hayes, A. F., Lunney, C. A., McFall, M., & Uddo, M. (2006). Longitudinal analysis of the relationship between symptoms and quality of life in veterans treated for posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology, 74*, 707 – 713.

Schnurr, P. P., Lunney, C. A., Bovin, M. J., & Marx, B. P. (2009). Posttraumatic stress disorder and quality of life: Extension of findings to veterans of the wars in Iraq and Afghanistan. *Clinical Psychology Revew, 29,* 727 – 735.

Schwartz, B. L., Hastroudi, S., Herting, R. L., Schwartz, P., & Deutsch, S. I. (1996). D-cycloserine enhances implicit memory in Alzheimer patients. *Neurology, 46*, 420-424.

Seghal, S. N., Baker, H., & Vezina, C. (1975). Rapamycin (AY-22, 989), a new antifungal antibiotic. *The Journal of Antibiotics, 28*, 721 – 726.

Shalev, A. Y. (2000). Measuring outcome in posttraumatic stress disorder. *Journal of Clinical Psychiatry, 61*(Suppl. 5), 33 – 42.

Shalev, A. Y. (2001). What is posttraumatic stress disorder? *Journal of Clinical Psychiatry, 62*(suppl 17), 4-10.

Shimamura, A. P. (1996). Memory and frontal lobe function. In M. S. Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 803-814). Cambridge, MA: MIT Press.

Shimamura, A. P. (2002). Memory retrieval and executive control processes. In D.T. Stuss & R. T. Knight (Eds.), *Principles of frontal lobe function* (pp. 1009 – 1020). Cambridge, MA: MIT Press.

Shucard, J. L., McCabe, D. C., & Szymanski, H. (2008). An event-related potential study of attention deficits in posttraumatic stress disorder during auditory and visual Go/NoGo continuous performance tasks. *Biological Psychology, 79*(2), 223 – 233. Doi:10.1016/j.biopsycho.2008.05.005

Silver, J. M., McAllister, T. W., & Yudofsky. S. C. (Eds.). (2005). *Textbook of traumatic brain injury.* Arlington, VA: American Psychiatric Publishing.

Smolewski, P. (2006). Recent developments in targeting the mammalian target of rapamycin (mTOR) kinase pathway. *Anti-Cancer Drugs, 17*, 487 – 494.

Stein, M. B., Kennedy, C. M., & Twamley, E. W. (2002). Neuropsychological function in female victims of intimate partner violence with and without posttraumatic stress disorder. *Biological Psychiatry, 52*, 1079-1088.

Stein, M. B., & McAllister, T. W. (2009). Exploring the convergence of posttraumatic stress disorder and mild traumatic brain injury. *American Journal of Psychiatry, 166*, 768 – 776.

Sutker, P. B., & Allain, Jr., A. N. (1996). Assessment of PTSD and other mental disorders in World War II and Korean Conflict POW survivors and combat veterans. *Psychological Assessment, 8*, 18 – 25.

Swiech, L., Perycz, M., Malik, A., & Jaworski, J. (2008). Role of mTOR in physiology and pathology of the nervous system. *Biochimica et Biophysica Acta, 1784,* 116 – 132.

Tang, S. J., Reis, G., Kang, H., Gingras, A. C., Sonenberg, N., & Schuman, E. M. (2002). A rapamycin-sensitive signaling pathway contributes to long-term synaptic plasticity in the hippocampus. *Proceedings of the National Academy of Sciences USA, 99*, 467 – 472.

Taniellen, T. & Jaycox, L. (Eds.). (2008). *Invisible wounds of war: Psychological and cognitive injuries, their consequences, and services to assist recovery.* Santa Monica, CA: RAND Corporation.

Tariot, P. N., Farlow, M. R., Grossberg, G. T., Graham, S. M., McDonald, S., & Gergel, I. (2004). Memantine treatment in patients with moderate to severe Alzheimer Disease already receiving Donepezil: A randomized controlled trial. *Journal of the American Medical Association, 291*, 317 – 324.

Tsang, C. K., Qi, H., Liu, L. F., Zheng, X. F. (2007). Targeting mammalian target of rapamycin (mTOR) for health and diseases. *Drug Discovery Today, 12*, 112 – 124.

Twamley, E. W., Hami, S., & Stein, M. B. (2004). Neuropsychological function in college students with and without posttraumatic stress disorder. *Psychiatry Research, 126*, 265 – 274.

Uddo, M., Vasterling, J., Brailey, K., & Sutker, P. (1993). Memory and attention in combat-related post-traumatic stress disorder (PTSD). *Journal of Psychopathological and Behavioral Assessment, 15*(1), 43 – 52.

Vasterling, J. J., & Brailey, K. (2005). Neuropsychological findings in adults with PTSD. In J. J. Vasterling & C. R. Brewin (Eds.), *Neuropsychology of PTSD* (pp. 178 – 207). New York: The Guilford Press.

Vasterling, J. J., Brailey, K., Constans, J. I., & Sutker, P. B. (1998). Attention and memory dysfunction in posttraumatic stress disorder. *Neuropsychology, 12*(1), 125 – 133.

Vasterling, J. J., Duke, L. M., Brailey, K., Constans, J. I., Allain, A.N., Jr., & Sutker, P. B. (2002). Attention, learning, and memory performances and intellectual resources in vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology, 16*(1), 5 – 14. doi: 10.1037//0894-4105.16.15

Vermetten, E., Vythilingam, M., Southwick, S. M., Charney, D. S., & Bremner, J. D. (2003). Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. *Biological Psychiatry, 54,* 693 – 702.

Vignot, S., Faivre, S., Aguirre, D., & Raymond, E. (2005). mTOR-targeted thereapy of cancer with rapamycin derivatives. *Annual Oncology, 16*, 525 – 537.

Walter, K. H., Palmieri, P. A., Gunstad, J. (2010). More than symptom reduction: Changes in executive function over the course of PTSD treatment. *Journal of Traumatic Stress, 23*(2), 292 – 295.

Warden, D. (2006). Military TBI during the Iraq and Afghanistan wars. *The Journal of head Trauma Rehabilitation, 21*, 398 – 402.

Wilcox, G., Mobius, H. K., & Stoffler, A. (2002). A double-blind, placebo controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). *International Clinical Psychopharmacology, 17*, 297 – 305.

Wolfe, J. & Charney, D. S. (1991). Use of neuropsychological assessment in posttraumatic stress disorder. *Psychological Assessment: A Journal of Consulting and Clinical Psychology, 3,* 573 – 580.

Woolley, C. S., Gould, E. McEwen, B. S. (1990). Exposure to ecvess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. *Brain Research, 531,* 225-231.

Xydakis, M. S., Fravell, M. D., Nasser, K. E., & Casler, J. D. (2005). Analysis of battlefield head and neck injuries in Iraq and Afghanistan. *Otolarynology – Head and Neck Surgery, 133*, 497 – 504.

Yehuda, R., Keefe, R., Harvey, P. D., Levengood, R. A., Gerber, D. K., Geni, J., & Siever, L. J. (1995). Learning and memory in combat veterans with posttraumatic stress disorder. *American Journal of Psychiatry, 152*(1), 137 – 139.

Yehuda, R., & McFarlane A. C. (1995). Conflict between current knowledge about posttraumatic stress disorder and its original conceptual basis. *American Journal of Psychiatry, 152,* 1705 – 1713.

Table 1.

Description of RBANS Indexes

Index	Description
Immediate Memory	Demonstrates the ability to remember information immediately after it is presented.
Visuospatial/Constructional	Demonstrates the ability to recognize spatial relations and to create a spatially accurate copy of a drawing.
Language	Demonstrates the ability to respond verbally by retrieving and naming learned material.
Attention	Demonstrates the capability to remember and manipulate visually and orally presented information in short-term memory.
Delayed Memory	Demonstrates anterograde memory capabilities.
Total Scale	A total score that is generated by summing the 5 previous index scores.

Table 2.

Description of RBANS Subtests

Index	Subtest	Description
Immediate Memory	List Learning	The examiner reads a list of ten semantically unrelated words and the examinee is asked to recall as many words as he can. The procedure is repeated four times.
	Story Memory	The examiner reads a short story and the examinee is asked to retell the story from memory. The procedure is repeated twice.
Visuospatial/ Constructional	Figure Copy	The examinee is shown a complex geometric drawing. He is then asked to make a precise copy while the drawing remains displayed.
	Line Orientation	The examinee is shown a drawing of 13 equal lines radiating out from a single point to form a semicircular fan-shape. The lines are numbered 1-13. Below the drawing are two lines that match two of the lines from the drawing and the examinee is asked to identify which of the two lines they match. Ten trials with different sets of test lines are given.
Language	Picture Naming	The examinee is shown a series of pictures and is asked to name the objects in each one.
	Semantic Fluency	The examinee is given 60 seconds to name as many exemplars as possible from a given category.

(continued)

Index	Subtest	Description
Attention	Digit Span	The examinee is read a string of digits and asked to repeat the digits in the same order. The length of the digit string increases with each trial.
	Coding	The examinee is given a page filled with rows of boxes that are randomly assigned a number ranging from 1 to 9. A key is positioned at the top of the page with simple geometric shapes beneath each of the numbers of 1 through 9. The examinee is asked to use the key to draw the shape corresponding to each numbered box for as many as he can complete in 90 seconds.
Delayed Memory	List Recall	The examinee is asked to recall the list of 10 words from the List Learning subtests.
	List Recognition	The examinee is read 20 words (10 targets and 10 distracters) and asked to indicate whether each word was on the word list from the List Learning subtest.
	Story Memory	The examinee is asked to retell the story from the Story Memory subtest.
	Figure Recall	The examinee is asked to draw the figure from the Figure Copy subtest from memory.

Table 3.

Description and Assessments for Study Sessions

Session	Description	Assessments
1	Baseline - Assessments	LEC **CAPS** PCL **QIDS** **RBANS-A**
2	Treatment 1 – Rapamycin/placebo administration and script preparation	PCL QIDS
3	Treatment 2 – Script-driven traumatic memory reactivation	PCL QIDS
4	1-Month Follow-up – Assessments	**CAPS** PCL **QIDS** **RBANS-B**
5	3-Month Follow-Up – Assessments	CAPS PCL QIDS

Note. Highlighted measures were used in the smaller study. Abbreviations: LED – Life Events Checklist, CAPS – Clinician Administered PTSD Scale, PCL – PTSD Checklist, QIDS – Quick Inventory of Depressive Symptomatology, RBANS – Repeatable Battery for the Assessment of Neuropsychological Status.

Table 4.

Demographic Characteristics

Characteristic	Control Group (n = 23)	Rapamycin Group (n = 27)	Total Sample (n = 50)
Age (M±SD)	42.2 (15.7)	43.67 (14.76)	43(14.9)
Education (M±SD)	13.61 (1.4)	14.07 (1.54)	13.86 (15)
Ethnicity (n [%])			
White	13 (56.5%)	11 (40.7%)	24 (48%)
African-American	7 (30.4%)	8 (29.6%)	15 (30%)
Hispanic (white)	1 (4.3%)	2 (7.4%)	3 (6%)
Hispanic (black)	0	4 (14.8%)	4 (8%)
Native American	0	1 (3.7%)	1 (2%)
Other	2 (8.7%)	1 (3.7%)	3 (6%)
Marital Status (n [%])			
Married	12 (52.2%)	15 (55.6%)	27 (54%)
Never Married	3 (13%)	3 (11.1%)	6 (12%)
Living with partner	1 (4.3%)	3 (11.1%)	4 (8%)
Divorced	6 (26.1%)	3(11.1%)	9 (18%)
Separated	1 (4.3%)	2 (7.4%)	3 (6%)
Widowed	0	1 (3.7%)	1 (2%)
Employment Status (n [%])			
Full-time employed	6 (26.1%)	4 (14.8%)	10 (20%)
Part-time employed	4 (17.4%)	2 (7.4%)	6 (12%)
Retired	6 (26.1%)	5 (18.5%)	11 (22%)
Unemployed	5 (21.7%)	11 (40.7%)	16 (32%)
Other	2 (8.7%)	5 (18.5%)	7 (14%)
Branch of Service (n [%])			
Air Force	1 (4.3%)	0	1 (2%)
Army	14 (60.9%)	18 (66.7%)	32 (64%)
Marines	6 (26.1%)	5 (18.5%)	11 (22%)
Navy	1 (4.3%)	2 (7.4%)	3 (6%)
Multiple	1 (4.3%)	2 (7.4%)	3 (6%)

(continued)

Characteristic	Control Group (n = 23)	Rapamycin Group (n = 27)	Total Sample (n = 50)
Service Era (n [%])			
Vietnam	8 (34.8%)	9 (33.3%)	17 (34%)
Desert Storm/Bosnia /Somalia	0	6 (22.2%)	6 (12%)
OEF/OIF	15 (65.2%)	12 (44.4%)	27 (54%)

Table 5.

Means and Standard Deviations of Study Measures

Study Measure	Baseline	1-Month Follow-Up
CAPS (M ±SD)		
Placebo Group (*n* = 23)	71.78 (15.53)	64.70 (18.27)
Rapamycin Group (*n* = 27)	70.22 (15.98)	58.37 (22.53)
RBANS (M±SD)		
Placebo Group (*n* = 23)	91.70 (12.51)	91.83 (14.77)
Rapamycin Group (*n* = 27)	92.11 (13.74)	92.15 (14.74)
QIDS (M±SD)		
Placebo Group (*n* = 23)	13.61 (4.46)	11.65 (3.81)
Rapamycin Group (*n* = 27)	14.37 (3.82)	11.37 (4.96)