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PTSD SYMPTOM SEVERITY AND NEUROCOGNITIVE PERFORMANCE AS A FUNCTION OF COMBINED TMS AND IMAGINAL EXPOSURE IN OIF/OEF COMBAT VETERANS WITH TREATMENT RESISTANT PTSD

by

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A Dissertation Submitted to the Faculties of Eastern Virginia Medical School, Norfolk State University, and Old Dominion University
in Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY

CLINICAL PSYCHOLOGY

VIRGINIA CONSORTIUM PROGRAM IN CLINICAL PSYCHOLOGY
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ABSTRACT

PTSD SYMPTOM SEVERITY AND NEUROCOGNITIVE PERFORMANCE AS A FUNCTION OF COMBINED TMS AND IMAGINAL EXPOSURE IN OIF/OEF COMBAT VETERANS WITH TREATMENT RESISTANT PTSD

Katharine Surella Seagly
Virginia Consortium Program in Clinical Psychology, 2015
Director: Dr. Serina A. Neumann

Posttraumatic Stress Disorder (PTSD) is a commonly occurring mental health diagnosis, and is particularly prevalent in combat veterans. Although there has been some success treating PTSD with various forms of therapy, many cases remain refractory to the current standard of care. This pilot study combines transcranial magnetic stimulation (TMS) to the right dorsolateral prefrontal cortex (DLPFC) and the supplementary motor area (SMA) with a standardized exposure protocol for the treatment of chronic, treatment-resistant PTSD. The aims are to (1) determine if the treatment is safe and well tolerated, (2) determine if PTSD and concomitant depression and anxiety symptoms improve, and (3) determine if executive functioning and memory improve. Results indicated the treatment was safe and well tolerated, and improvements were seen across psychological symptoms. Neurocognitively, improvements were seen in executive functioning but not in non-executive memory. Statistically significant results must be interpreted with caution due to the likelihood of sampling error associated with a small sample size. However, clinical results were striking, with six of the seven participants no longer meeting criteria for PTSD by the end of the study. Clinical results for this pilot study were promising and warrant further investigation with larger sample sizes utilizing a RCT model to confirm and expand upon these preliminary findings.

This dissertation is dedicated to all who have served in the United States Armed Forces, and most particularly to the combat Veterans who participated in this study. May there come a day when no man, woman or child must face what you have so bravely endured.

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There are so many, but I know you want to get on to the substantive piece, so I will try to be brief! First, I wish to acknowledge the entire Consortium family—each of you taught me, pushed me when I needed urging, reassured me when I needed comfort, made me believe I could actually do this. I also wish to acknowledge my parents. Mom, you have always stood by me; you have been my defender when I did not deserve a defense; you believe me to be beyond comparison, which is laughably inaccurate, but such a loving gesture; you love me as only a mother could—thank you Mom. Dad, you taught me to love learning for the sake of learning, not to see it as merely a means to an end. When I majored in philosophy, you encouragingly said, "Philosophy is the jewel in the crown of the liberal arts" when most parents would have said, "How are you going to make money??" This love of learning you instilled has carried me through my on again, off again, then on again educational process, culminating in this dissertation, and my doctorate—thank you Dad. I wish to acknowledge my dissertation committee for their time and effort in helping me to make this little study into a substantive product. Dr. Neumann, you have consistently gone above and beyond in every possible regard. You were right there beside me, bearing witness to the tragedies of war these Veterans withstood—you supported me so I could support them. Finally, I wish to acknowledge my husband and my son. Joe, every day I am with you I feel as though I've won the lottery. I don't know what I did to deserve you so I will have to chalk it up to dumb luck, and thank the universe that I have been so lucky. At last, my dearest Harry, in truth this is all for you. Every second of every day of my life, you make it all worthwhile.

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CHAPTER 1

INTRODUCTION

Posttraumatic Stress Disorder (PTSD) occurs in as many as one-third to one-half of those exposed to traumatic events (American Psychiatric Association [APA], 2000), and is particularly prevalent in combat veterans (United States Department of Veterans Affairs, 2011). Although there has been some success treating PTSD with various forms of therapy, up to 58% of cases are refractory to the current standard of care (Foa, Keane, Friedman & Cohen, 2009; Schnyder, 2005). In addition to the emotional and psychological dysfunction experienced with PTSD, many patients also undergo a debilitating decline in neurocognitive functioning (Polak, Witteveen, Reitsma, & Olff, 2012; Uddo, Vasterling, Brailey, & Sutker, 1993).

Initial functional neuroimaging research on PTSD showed increased oxygen perfusion in the right prefrontal cortex as participants were retold their traumatic events (Rauch, van der Kolk, Fisler & Alpert, 1996). This finding was replicated in most subsequent studies (Lanius, Blugm, Lanius, & Pain, 2006; McCann et al., 1998; Post, Weiss, Smith, Li, & McCann, 1997), resulting in the common understanding that right-sided activity in PTSD is associated with the role of the right hemisphere in anxiety and other PTSD symptomatology (Ousch et al., 2009; Rauch, van der Kolk, Fisler, & Alpert, 1996; Simmons, Matthews, Stein, & Paulus, 2004). More recent research has also implicated an over-active supplementary motor area (SMA) in PTSD symptom maintenance (Shaw et al., 2009; Whalley, Kroes, Marijn, & Huntley, 2013). It follows then that low-frequency transcranial magnetic stimulation (TMS), a means of decreasing perfusion and cortical neuronal activity (Hoffman & Cavus, 2002; Huang, Edwards,

Bhatia, & Rothwell, 2004; Speer et al., 2000) applied to the right prefrontal cortex as well as the SMA would likely improve functional brain abnormalities associated with PTSD.

Due to established models of PTSD as a malfunction in fear extinction (Berkowitz, Coplan, Reddy & Gorman, 2007; Martel et al., 2012; Yehuda & LeDoux, 2007), it is likely to be particularly important to bring the neural circuits and the autonomic arousal involved in the conditioned fear "on-line" when trying to extinguish the fear response. One method for bringing the conditioned fear on-line is through imaginal exposure. Imaginal exposure is used to treat PTSD by exposing patients to memories of their traumatic events in a safe, controlled setting in order to desensitize them to the trauma and help them to learn that they are no longer in danger (Cahil & Foa, 2005). As such, combining low-frequency TMS and imaginal exposure to treat PTSD may be more effective than conducting either treatment individually.

The first aim of the present study is to investigate the safety and efficacy of combined TMS and prolonged imaginal exposure. The goal of this aim is to provide information regarding the utility of TMS as an additional modality of treatment for PTSD. The second aim of this study is to examine changes in neurocognitive functioning from pre- to post-treatment. The rationale for this second aim stems from literature indicating that PTSD is often accompanied by a decline in cognitive abilities, particularly in the areas of memory and executive functioning (Polak et al., 2012; Uddo et al., 1993).

PTSD Defined

It is well-documented in the scientific literature that traumatic events can lead to symptoms of PTSD (American Psychiatric Association, 2013; Brewin, Andrews, & Valentine, 2000; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). The more

prolonged and more severe a traumatic event, the more likely the person exposed will exhibit symptoms. According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; APA, 2000)[1], PTSD is a group of symptoms that follow "exposure to actual or threatened death, serious injury, or sexual violence." This exposure can include experiencing, witnessing, or learning about the traumatic event (Criterion A). A diagnosis of PTSD also requires the following: persistent re-experiencing of the event, such as distressing memories, dreams, or flashbacks (Criterion B); persistent avoidance of stimuli associated with the traumatic event, which may include avoidance of memories, thoughts, or feelings about the event, or avoidance of external reminders such as people or places (Criterion C); persistent symptoms of increased arousal, such as irritability and angry outbursts, hypervigilance, problems with concentration, and an exaggerated startle response (Criterion D). These symptoms must have been present for more than one month (Criterion E) and must cause significant distress or impairment (Criterion F; APA, 2000).

PTSD Prevalence

Community-based studies indicate that the approximate lifetime prevalence for PTSD is 8.7% of the adult population in the United States, or about 27 million people (APA, 2013). Women are more than twice as likely as men to have PTSD at some point in their lives according to the National Comorbidity Survey Replication (NCS-R; Kessler, Berglund, Demler, Jin, Merikangas & Walters, 2005), however combat-related PTSD is much more prevalent in men as the U. S. Department of Defense has only recently

[1] The CAPS for the DSM-V was not yet available at the start of the present study. As such, DSM-IV criteria were used for the diagnosis. Clinically, all participants also met criteria for a DSM-V diagnosis of PTSD, which overlaps a great deal with the DSM-IV diagnosis, but again, a standardized, objective measure for these criteria was unavailable.

permitted women to serve in combat positions (Roulo, 2013). Studies of individuals who are considered high-risk for PTSD (i.e., those exposed to specific traumatic events) reveal variable findings with prevalence rates ranging from one-third to more than one-half of those exposed to rape, military combat and captivity, and ethnically or politically motivated internment and genocide (APA, 2000). According to the most recent estimate from the United States Department of Veterans Affairs, approximately 11-20% of Veterans of the Iraq and Afghanistan wars (Operations Iraqi and Enduring Freedom; OIF and OEF respectively), have been diagnosed with PTSD (2011). This constitutes a 2-11% increase over rates in the general population.

Factors other than gender and combat experience increase potential for PTSD risk. Those with low socioeconomic status (SES) are more likely to develop PTSD (Chiu, de Roon-Cassini, & Brasel, 2011). However, research also shows that PTSD has negative consequences for income and employment, thus contributing to a decline in SES among those with this diagnosis. A lifetime diagnosis of PTSD is associated with a nearly 50% lower probability of current employment (Savoca & Rosenheck, 2000), and Veterans with PTSD are three times more likely to be unemployed (Zatzick et al., 1997). Thus, the effects of PTSD extend to the realm of occupational dysfunction and financial strain.

Standard of Care for PTSD

The standard treatments available for PTSD typically include medication therapy, which has limited efficacy as compared to psychotherapy (Van Etten & Taylor, 1998), as well as exposure-based and cognitive therapies, such as Prolonged Exposure (PE), Cognitive Processing Therapy (CPT), and Eye Movement Desensitization and

Reprocessing (EMDR; Benedek, Friedman, Zatzick, & Ursano, 2009; Cloitre, 2009; Foa et al., 2009). The American Psychological Association [APA] Division 12 lists PE and CPT as having "strong research support" as evidenced by two or more randomized controlled trials indicating their effect (APA, 2013). EMDR is considered "controversial" as numerous studies have shown the mechanism of action to be the exposure component rather than the eye movement (APA, 2013). Briefly, as a comparison to the PE utilized in the present study, the basic premise of CPT contends that changing the content of cognitions about a trauma can impact emotional and behavioral responses to the trauma. Essentially, CPT is a cognitive therapy that focuses initially on the question of why the trauma occurred and then the effects of the trauma on the clients' beliefs about themselves, others, and the world through the use of progressive worksheets. It is typically administered in 12 90-minute sessions (APA, 2013). PE, described in detail in the procedures section, involves repeated exposure to trauma-related thoughts, feelings, and situations as this can help reduce the power they have to cause distress. Essentially, PE consists of imaginal exposures, which involve recounting the traumatic memory and processing the revisiting experience, as well as in vivo exposures in which the client repeatedly confronts trauma-related stimuli that were safe but previously avoided. It is typically administered in 8-15 sessions lasting 60-120 minutes each (APA, 2013). And so, CPT attempts to break into the cycle of PTSD maintenance at the level of cognition whereas PE attempts to break into the cycle at the level of experience. EMDR is not considered here due to consistent evidence that it is just an alternate version of prolonged exposure therapy (APA, 2013).

While some patients find these treatments to be effective, studies of cognitive-based therapies show drop-out rates around 20%. Furthermore, the current treatment options have a limited effect on PTSD symptoms. Up to 58% of those who complete treatment continue to meet criteria for a PTSD diagnosis even after treatment, while only 32–66% obtain a satisfactory level of functioning (Foa et al., 2009; Schnyder, 2005). Thus, PTSD remains a chronic illness for many individuals, despite treatment. Those with chronic PTSD also have high rates of psychiatric and medical comorbidities (Jacobsen, Southwick, & Kosten, 2001; McFarlane, 2010), as well as suicidality (Panagioti, Gooding & Tarrier, 2012). Due to the prevalence and level of debilitation effected by this diagnosis, the severity of comorbidities, and given that a large number of patients do not recover with the current standard of care, it is imperative that we continue to extend the knowledge base on effective treatment options for PTSD.

Neurobiological Substrates of PTSD

The Dorsolateral Prefrontal Cortex. The dorsolateral prefrontal cortex (DLPFC) is partially responsible for executive functions such as integration of sensory and mnemonic information, and the regulation of intellectual function and action, particularly in relation to impulse control. Damage to the DLPFC can result in the problems with affect, social judgment, executive memory, abstract thinking, and intentionality (Zelazo & Muller, 2002), all of which are criteria for, or often accompany, PTSD (APA, 2013). Additionally, a specific pattern of prefrontal and limbic abnormalities in PTSD is suggested by neuropsychological tests sensitive to frontal lobe damage. Specifically, research shows impaired performance on tests reflecting abnormalities of the dorsolateral prefrontal cortex, the orbitofrontal cortex, and the limbic

system in general (Bremner et al., 1995; Cohen et al., 2004; Koenen, et al., 2001; Vasterling, Brailey, Constans, & Sutker, 1998).

Neuroimaging studies have also shown that patients with PTSD have increased blood flow and glucose utilization in right frontal, limbic, and paralimbic brain structures, including the right DLPFC, particularly when they are recalling the traumatic event associated with their symptoms (Lanius et al., 2006; McCann et al., 1998; Post, Weiss, Smith, Li & McCann, 1997). When considered together, these findings suggest that right frontal, limbic and paralimbic structures are closely associated with PTSD abnormalities and could potentially be the target of neurobiological treatment strategies.

The Amygdala. Amygdala responsivity has been shown to be positively associated with PTSD symptom severity in five independent studies (Armony, Corbo, Clément, & Brunet, 2005; Pissiota et al., 2002; Protopopescu et al., 2005; Rauch et al., 1996; Shin et al., 2004). When considering the role of the amygdala in PTSD, it is helpful to think of associative learning responses. For instance, a soldier might react with arousal and fear (the unconditioned response [UCR]) to traumatic experiences in combat, which would serve as the unconditioned stimulus (UCS). As time goes by, the soldier may continue to exhibit arousal and fear responses in the absence of traumatic events (the conditioned response [CR]). The response may be elevated when he encounters specific environmental cues that he associates with the previous trauma (the conditioned stimulus [CS]). This model applying associative learning to PTSD converges with both animal and human studies that point to the amygdala as one of the principal structures necessary for fear learning.

Studies involving lesioning, electrical stimulation, and site-specific pharmacology methods show the amygdala receives information about both unconditioned and conditioned stimuli and is responsible for integrating this information and then activating fear responses (Kaplan & Moore, 2011; Kim & Jung, 2006). Sensory pathways usually extend to the amygdala after processing from associative cortical areas (McDonald, 1998). Sensory information is then transported to the basolateral nuclei of the amygdala. This is where synapses are strengthened (or weakened) over time, producing CS-UCS associations. The basolateral nuclei are connected to the central nucleus of the amygdala, the primary fear production structure. This allows the newly learned fear association to influence autonomic and motor centers involved in fear responses, including the supplementary motor area (SMA; Davis, 2006; Kim & Jung, 2006; Pape & Pare, 2010).

The Supplementary Motor Area. While the amygdala cannot be directly stimulated via TMS, TMS has been shown to modulate activity in brain regions well beyond the locus of stimulation (Bohning et al., 2000; Cheeran, Koch, Stagg, Baig, & Teo, 2010; Ji et al., 1998). For example, direct stimulation of the primary motor cortex has been shown to affect the striatum (Strafella, Paus, Fraraccio, & Dagher, 2003). It is therefore likely that stimulation to the SMA will induce combined action on cortical and subcortical structures (stimulated transsynaptically). As noted above, afferent connections exist from the SMA, partially responsible for integration of incoming sensory information and subsequent behavioral responses, to the amygdaloid nucleus (Davis, 2006; Kim & Jung, 2006; Jürgens, 1984). Thus, it is theorized that low-frequency TMS to the SMA will aid in retraining the neural pathways between the SMA

and the amygdala to fire less frequently, thereby decreasing fear and arousal associated with amygdala activation.

Further support for the SMA's role in PTSD comes in the form of a recent fMRI investigation of posttraumatic flashbacks. Researchers found that the contrast of flashbacks versus ordinary episodic memories in PTSD was associated with increased activation in sensory and motor areas, including the SMA (Whalley, Kroes, Marijn, & Huntley, 2013). It is also noteworthy that low-frequency stimulation to the SMA decreases anxiety-related symptoms in disorders such as Obsessive Compulsive Disorder (Mantovani, Simpson, Fallon, Rossi, & Lisanby, 2009). Finally, a study on working memory deficits in PTSD showed activation in of the SMA in PTSD participants, but not in controls, during working memory tasks (Shaw et al., 2009). While the role of the SMA is not yet fully understood, these findings are further indication that, along with the amygdala, the SMA is over-active in those with PTSD.

The Hippocampus. The hippocampus, a part of the limbic system that plays important roles in the consolidation of information from short-term memory to long-term memory, has been shown in animal studies to be essential in contextual fear conditioning, and thus in PTSD. Communication between the hippocampus and the amygdala is both direct and indirect through the prefrontal cortex (Pape and Pare, 2010). Thus, it is likely that TMS can affect hippocampal activity through prefrontal cortex stimulation, and also through stimulation of the SMA via pathways through the amygdala. Lesion studies have shown that the hippocampus is required for the renewal of conditioned fear responses (Kim & Jung, 2006; Maren, 2008). As such, it is probable that the hippocampus plays a vital part in the maintenance of PTSD-associated fear and arousal.

Most neuroimaging studies of the hippocampus in PTSD have examined hippocampal structure rather than function. The primary finding is of decreased hippocampal volumes in PTSD, compared to either trauma-exposed control subjects (Bremner et al., 1995; Childress et al., 2013; Gurvits et al., 1996; Gilbertson et al., 2002) or trauma-unexposed healthy subjects (Bremner et al., 2003; Childress et al., 2013; Wignall et al., 2004; Winter & Irle, 2004). A few studies in the literature have examined hippocampal function in PTSD. Blood flow in the hippocampus and parahippocampal gyrus was significantly positively correlated with PTSD symptom severity (Shin et al., 2004), which is consistent with findings of higher activity in the hippocampal region at rest and during an auditory continuous performance task in those with PTSD (Sachinvala, Kling, Suffin, & Cohen, 2000; Semple et al., 2000). Finally, a positive correlation was found between flashback intensity and regional cerebral blood flow in the perihippocampal region in patients with chronic PTSD (Ousch et al., 2009).

Other Notable Findings. In a study examining the effects of electrical stimulation during brain surgery, it was found that the temporal cortex is yet another brain region associated with the reliving of past experiences (Criteria B for PTSD; Rosenberg et al., 2002). Further, a relation between flashbacks among patients with PTSD and increased brain circuitry activity between the temporal and parieto-occipital lobe has been identified. Using Magnetoencephalography (MEG), a non-invasive technique that measures magnetic fields in the brain, researchers uncovered significant differences between signals in the temporal and parieto-occipital right hemispheric areas, particularly in the right superior temporal gyrus (Cohen et al., 2004). Later research has not replicated these findings, but instead found increased brain circuitry activity in the

sensory and motor areas, as mentioned previously (Whalley, Kroes, Marijn, & Huntley, 2013).

All of these various alterations in regional brain activity are thought to be related, in part, to the distressing emotional symptoms associated with traumatic memories and concomitant abnormalities in autonomic nervous system (ANS) function as well as in endocrine function stemming from the hypothalmic-pituitary-adrenal (HPA) axis (Cohen, et al., 2000; Yehuda, 2007). Thus, it is likely that those with PTSD also have increased heart rates and elevated cortisol levels. As TMS is a focused, non-invasive treatment procedure shown to stabilize neuron function and metabolism in the brain, is likely to alleviate PTSD symptoms and normalize ANS and HPA axis function.

TMS Background

TMS was first applied to humans in the 1890s and found to induce phosphenes (a sensation of flickering light), vertigo, and syncope. Scientists in the mid-20th century used this early data to understand that the application of an electromagnetic coil to the brain could induce visual changes and motor activity (George et al., 2007). By 1985, the technology was being used by neurologists to study the conduction of motor impulses between the central and peripheral nervous systems. Using TMS, Barker and colleagues were able to stimulate the motor cortex of individuals and observe the subsequent motor response (Barker, 1991). The fact that this was achieved painlessly and without the need for loss of consciousness suggested a broader role for TMS in the field of neurostimulation.

In 1987, while stimulating the motor cortex, Bickford was the first to illustrate an improvement in mood in healthy subjects (Bickford, Guidi, Fortesque & Swenson, 1987).

Neurologists and psychiatrists across Europe and the United States began to view TMS as both a research tool and as a novel treatment modality. Groundbreaking works by Dr. Pasqual-Leone at Harvard Medical School, Dr. Avery at the University of Washington, Dr. George from the Medical College of South Carolina, Dr. Wassermann with the NIH, and Drs. Lisanby and Mantovani at the New York State Psychiatric Institute have demonstrated a breadth of evolving possibilities while offering significant data to support the use of TMS for treatment of depression, anxiety disorders, and even psychosis (George et al., 2007). When compared with other forms of neuromodulation such as electroconvulsive therapy (ECT), deep brain stimulation (DBS), and vagal nerve stimulation (VNS), TMS stands out as the least invasive in that it does not require anesthesia, surgery or installed devices.

TMS is currently FDA approved for the treatment of major depression in people who have failed at least one medication trial. High-frequency, repetitive TMS is thought to balance out hypometabolism often seen with MDD and facilitate cortical responses in the left prefrontal cortex (Pascual-Leone, Catalá, & Pascual-Leone, 1996; Pascual-Leone, Valls-Solé , Wassermann, & Hallett, 1994). Its efficacy in populations of patients with TRD has been demonstrated since the early 1990s. George et al. (1996), Pascual-Leone et al. (1994), and Triggs et al. (1999) have all demonstrated a significant reduction in scores on the Hamilton Depression Rating Scale (HAM-D) and Beck Depression Inventory (BDI) in patients with severe TRD.

More recent studies have compared the efficacy of TMS with ECT (Grunhaus et al., 2000; Schulze-Rauschenbach, Harms, Schlaepfer, Maier, Falkai & Wagner, 2005). Both Grunhaus et al. and Schulze-Rauschenbach et al. demonstrated similar response

rates between the two treatment modalities and underscored the improved side effect profile of TMS when compared to ECT. In a double-blinded, sham-controlled[2] study with treatment-resistant patients, Avery et al. (2006) demonstrated significant response and remission rates in participants receiving only 15 days of stimulation of the left dorsolateral prefrontal cortex (DLPFC). Finally, the results of a recent NIMH-sponsored, multi-center trial show TMS to be an efficacious treatment for TRD above and beyond the traditional standard of care (George et al., 2010; Kim, Pesiridou, & O'Reardon, 2009). These metabolic, biochemical, and self-reported mood changes have been correlated with behavioral changes using functional neuroimaging. Whether or not long-term structural changes occur is yet to be determined.

TMS Mechanism of Action

As opposed to other modalities of brain stimulation, such as electroconvulsive therapy (ECT), deep brain stimulation (DBS), and vagal nerve stimulation (VNS), TMS is non-invasive and relatively painless. The TMS device consists of an electrified magnetic resonance imaging (MRI)-strength magnet and an iron-core, figure-eight coil. A rapidly alternating magnetic field induces an electrical current that is discharged through the coil. As per Faraday's law, any rapidly alternating magnetic field can induce an electrical current in a conducting substance (Serway, Moses, & Moyer, 2005). As such, the charge is able to pass through the skull unimpeded and induce an electrical current in the brain. The current depolarizes neuronal membranes and can then alter

[2] Sham TMS is a term used to describe a range of procedures utilized as control conditions for TMS treatment studies. Sham TMS can include the use of a special sham coil that is similar in all regards to a TMS treatment coil, with the exception that it does not stimulate the cortex, thus double-blinding both the treater and the patient. Sham TMS can also be used to describe tilting the coil 90 degrees off of the scalp or stimulating at a different site. These options blind the patient to the condition but not the treater. All sham TMS procedures discussed in the literature review for the present study refer to the former type of sham condition; both treater and patient are blinded.

neuronal firing with subsequent modulation of neurotransmitter release. This modulation allows the strength of synapses between neurons to be increased or decreased depending on frequency of the TMS (Huerta & Volpe, 2009). This process can have many therapeutic effects, including alterations in mood, cognition, and behavior (Kluger & Triggs, 2007; Lam, Chan, Wilkins-Ho & Yatham, 2008; Padberg & George, 2009). Further research examining the mechanism of action of TMS has shown it has an effect on gene expression (Cheeran, Koch, Stagg, Baig, & Teo, 2010), regional cerebral blood flow (Speer et al., 2000), neurotransmission (Strafella, Paus, Barrett, & Dagher, 2001), and neuroendocrine tone (Szuba et al., 2001). In essence, TMS exerts its clinical effect by upregulating (high frequency TMS) or downregulating (low frequency TMS) neuronal activity in a particular brain region (Kimbrell et al., 1999).

Effects of TMS on PTSD

Few studies have used TMS to treat PTSD. In the limited research available, patients with difficult to treat and chronic PTSD have benefited from TMS above and beyond the standard of care treatments available for this debilitating disorder (Boggio et al., 2010). However, research thus far has utilized several different protocols to treat PTSD. For instance, when repetitive TMS was applied to the left prefrontal cortex in patients with co-morbid PTSD and depression (at 1Hz or 5 Hz at 80% of motor threshold) there was a clinically significant antidepressant response in 9 out of the 12 patients, but researchers also found an improvement in core PTSD symptoms (Boggio et al., 2010). The authors stated that there may be dissociation between treating mood and core PTSD symptoms and it is therefore recommended that further research investigate other protocols using repetitive TMS.

In an earlier study, TMS (at 10 Hz and 80% of motor threshold) to the right prefrontal cortex was administered to 24 patients with PTSD under double-blind, placebo-controlled conditions, producing a significant reduction in PTSD symptomatology (Cohen, 2004). The most recently reported study using TMS to treat PTSD investigated the efficacy of 20 Hz repetitive TMS of either right or left dorsolateral prefrontal cortex (DLPFC) as compared to sham TMS in 30 participants (10 in each condition; Georgopoulos et al., 2010). Regardless of the frequency or intensity of the stimulation used in these studies, it seems that patients are benefiting from the stimulation either in improved mood, with high-frequency left-sided stimulation, or lower anxiety levels, with low-frequency right-sided stimulation. Furthermore, there is preliminary evidence that there is improvement in core PTSD symptoms above and beyond improvement in mood and generalized anxiety when either side is treated.

Finally, a recent study examining TMS as a method of fear extinction in rats lends support to the use of TMS for PTSD in humans. Baek, Chae, and Jeong (2012) administered high-frequency (10 Hz) TMS to the rats with the coil placed approximately 3 mm anterior to bregma and set tangentially to the sagittal axis. A control group received sham treatment. The rats treated with active TMS paired with a conditioned stimulus (based on an UCS of electrical shock) during extinction showed an enhancement in fear extinction over the sham group. Furthermore, this enhancement of fear extinction remained after 24 hours without further stimulation. The authors concluded that this finding suggests TMS paired with trauma-reminding stimuli enhances fear extinction. Thus it is likely that TMS in conjunction with exposure therapy may be useful for facilitating extinction memory in the treatment of PTSD.

Effects of Combined TMS and Therapy on PTSD

Only one study has examined the combined effects of TMS and therapy to treat PTSD (Ousch et al., 2009). Nine participants with chronic, treatment-refractory PTSD were studied in a placebo-controlled, crossover design of imaginal exposure therapy with low-frequency TMS (1 Hz) versus sham TMS. Participants received twenty 30-minute sessions of active or sham TMS to the right DLPFC in the first phase of the study, and then were switched to the remaining condition (sham or active) for the second phase. Active TMS showed a larger effect size of improvement for hyperarousal symptoms compared to sham. However, there was no difference between active TMS and sham for intrusion and avoidance symptoms. Ousch and colleagues also examined 24-hour urine and serum catecholamine and hormone levels, finding that increases in urinary norepinephrine and serum T4 were greater with active TMS compared with sham TMS. While these last findings did not have statistically significant *p*-values, they did show large effect sizes (Cohen's $d = 0.88$ and 1.43, respectively). It was not clear whether any patients were below the clinical threshold for PTSD post-treatment.

Unlike the present study, Ousch et al. did not stimulate the SMA. Further, the imaginal exposure procedure was different in that the participants could choose to speak about any past traumatic memory, or could choose to be silent during TMS. There was no information in the article detailing how many participants chose to be silent. The protocol for the present asked the participants to continually speak of their most traumatic military-related experience during each TMS session. It was believed that continual

exposure to their most traumatic event will best activate the circuitry that is maintaining their PTSD, and also wasthe best method for encouraging habituation to their trauma.

Effects of TMS on Neurocognitive Functioning

Executive Functioning. Results of studies examining pre- and post-TMS neurocognitive functioning are limited, but consistently show no adverse effects, and instead often demonstrate improved functioning (Bayan, 2014; Hufnagel, Claus, Brunhoelzl, & Sudhop, 1993; Pascual-Leone et al., 1993; Wassermann, 1996; Martis et al., 2003). In a study examining the effect of high-frequency TMS (20 Hz at 80% motor threshold) on executive functioning, Moser and colleagues (2002) administered either active (n = 9) or sham (n = 10) TMS targeted at the anterior portion of the left middle frontal gyrus. Patients in the active TMS group improved significantly on a test of cognitive flexibility and conceptual tracking (Trail Making Test–B). Triggs et al. (1999) found improvements on tests of executive functioning and attention after 10 days of high-frequency (20 Hz) TMS over left DLPFC. A study by Martis et al. (2003) provides further evidence of improved executive function post-TMS. TMS involved high-frequency left prefrontal stimulation delivered daily (Monday–Friday) using 10 Hz at 110% of motor threshold for 10 to 20 sessions. A battery of neurocognitive tests relevant to attention, working memory-executive function, objective memory, and motor speed were administered to participants before and after the TMS treatment. Following TMS, participants showed significant improvements in working memory-executive function, objective memory, and fine motor speed domains.

Memory. The Martis et al. study is only one of several findings indicating TMS can improve memory function. Little et al. (2000) examined the cognitive effects of both

low- (1 Hz) and high-frequency (20 Hz) TMS to the left DLPFC. Participants received stimulation at 80% of motor threshold five days a week for two weeks. Results showed modest, but significant improvements in visuo-spatial memory and verbal memory following high-frequency TMS and improvements in verbal memory following low-frequency TMS. Padberg et al. (1999) also found improvements in verbal memory scores following five days of high-frequency (10 Hz) and low-frequency (0.3 Hz) TMS over the left DLPFC. Lastly, Schulze-Rauschenbach and colleagues (2005) examined the neurocognitive effects of both ECT and TMS in 30 patients. Each group received a mean of 10 high-frequency (10 Hz) TMS sessions to the left DLPFC. Participants were assessed for memory, executive functioning, and attention pre- and one week post-treatment. Results showed consistent or improved cognitive performance and alleviated memory complaints for the TMS group. Further, TMS improved memory recall deficits and decreased memory complaints for the ECT group.

While the neurocognitive effects of TMS discussed above involved participants with TRD, these findings are relevant for those with PTSD as well because executive functioning and memory have both shown impairment in this population (Uddo, Vasterling, Brailey, & Sutker, 1993; Polak, Witteveen, Reitsma, & Olff, 2012). Moreover, as no studies were found examining the neurocognitive effects of TMS for PTSD, this is an area in which the knowledge base requires much expansion.

Imaginal Exposure Background

Anxiety and stress-related disorders can be treated by systematically exposing patients to the objects and reminders of events that induce anxiety or distress (Abramowitz, Deacon, & Whiteside, 2011; Echeburua, de Corral, Zubizarreta, &

Sarasua, 1997; Pitman et al., 1996). Imaginal exposure is used to treat PTSD by exposing patients to memories of the traumatic event in a safe and controlled setting, thereby desensitizing them to the event and teaching them that they are no longer in danger (Cahil & Foa, 2005; Foa, Hembree, & Rothbaum, 2007; Ruzek, Curran, Friedman, & Gusman, 2002). Surprisingly, animal research indicates that autonomic excitation, rather than relaxation and autonomic deactivation, improves the results of fear extinction training (Cain, Blouin, & Barad, 2004), which forms the theoretical basis of exposure therapy. Autonomic excitation has also been found to increase effectiveness of anxiety disorder treatment in humans (Craske and Mystkowski, 2006).

Furthermore, exposure therapy is by far the most rigorously scientifically supported treatment currently available for PTSD[3]. As mentioned previously, the APA Society of Clinical Psychology (Division 12) lists exposure therapy as having "strong research support" based on its proven effectiveness in five separate randomized trials (Foa et al., 1999; Foa et al., 2005; Foa, Rothbaum, Riggs, & Murdock, 1991; Keane, Fairbank, Caddell & Zimering, 1989; Resick, Nishith, Weaver, Astin & Feuer, 2002). Although other therapies have been deemed effective in the treatment of PTSD, exposure therapy has been proven effective in more clinical trials than the other available treatments. Expert Consensus Guidelines for the treatment of PTSD recommends exposure therapy as the quickest and most effective psychotherapy for the treatment of this disorder (Foa et al., 2009). In addition to exposure therapy's proven effectiveness, it is the most likely of the three established treatments for PTSD to produce autonomic excitation, thus activating the TMS-targeted circuitry.

[3] TMS is not currently FDA approved for the treatment of PTSD, and thus is not considered in this treatment comparison.

The Present Study

In general, clinical data are indicating that low frequency (i.e., 1 Hz) TMS stimulation leads to a decrease in regional cerebral blood flow, dampening hyperactivity seen in various brain regions (George et al., 1995; Kimbrell et al., 2002). Thus, it follows that the brain regions found to be hyperactive in PTSD patients, such as the right DLPFC and SMA, need to be dampened to normalize/stabilize the functioning of those neurons. Additionally, it was hypothesized that activating the circuits responsible for the PTSD symptoms, through imaginal exposure, while dampening their hyperactivity with TMS may be a more effective and direct treatment than TMS or prolonged exposure alone. However, there was no control group in the present study to examine this hypothesis. As such, any inferences drawn from comparing results of the present protocol to results of TMS or exposure protocols from previous studies are tentative and speculative at best.

Given these previous findings, the present study proposed to investigate the safety and efficacy of TMS as a treatment modality for PTSD while brain circuits related to PTSD symptoms are activated by the patient through repeated imaginal exposure. It was further hypothesized that neuropsychological functioning, particularly in the areas of memory and executive functioning, will improve following treatment.

Research Questions.

1. Is low-frequency TMS to the right DLPFC and the SMA combined with prolonged imaginal exposure associated with reduced PTSD symptoms and concomintant mood and anxiety symptoms (using the following scales: The Treatment Outcome PTSD Scale, the PTSD Checklist-Military, the Beck

Depression Inventory II, the Hamilton Depression Rating Scale, and the Beck Anxiety Inventory) after 16 treatment sessions, and one week post-treatment?

2. Is low-frequency TMS to the right DLPFC and SMA combined with prolonged imaginal exposure associated with improved neurocognitive functioning, including executive functioning, verbal memory, and visual memory (using the following scales: CNS Vital Signs, the California Verbal Learning Test Second Edition, the Rey Complex Figure Test, and the Wisconsin Card Sorting Test) after 16 treatment sessions, and one week post-treatment?

CHAPTER 2

METHOD AND PROCEDURE

Participants

Seven male participants between the ages of 22-55 who met DSM-IV criteria for PTSD took part in the study. While the original goal was to recruit ten participants, recruiting issues, including low response rates to fliers, brochures and radio advertisements, as well as difficulties in recruiting collaboration with the local Veteran's Administration Medical Center resulted in a smaller than expected sample size for this pilot study. It was required that the participants' PTSD be the result of combat trauma. Participants had failed to respond to at least one trial of medication or psychotherapy to treat PTSD and had symptoms of PTSD for at least one year. As such, they were considered to have chronic, treatment resistant PTSD. They were recruited from the Eastern Virginia Medical School Department of Psychiatry by study investigators. Prior to undergoing TMS treatment, a research team member informed each participant about the research opportunity and explained the study details in full. If the participant was interested in taking part, the clinical procedures were put in place, starting with the informed consent.

Exclusionary Criteria

Exclusionary criteria included the following: being female, having an uncontrolled significant medical illness (e.g., heart disease), pacemakers, cochlear implants, metal objects in the head or eyes, a history of seizures, psychotic disorders/symptoms, bi-polar disorder, active substance abuse/dependence issues, serious suicidal thinking or intent, medications that would decrease seizure threshold, family

history of epilepsy , bullet fragments or shrapnel within 30cm of the treatment coil, skull defects, recent stroke/intracranial bleed, conditions which may increase intracranial pressure, implanted medication pumps or intracardiac lines, ECT in the past 2 years, and previous magnetic brain stimulation treatment such as TMS. Participants were permitted to remain on medications that do not decrease seizure threshold, including psychotropic medications, so as not to exacerbate any pre-existing conditions. Medication changes were not made three months prior to the start of treatment or during the treatment protocol with the following exceptions: over-the-counter melatonin was added to one participant's regimen to aid with severe insomnia, and one participant chose to taper off his anti-depressant medication towards the end of treatment due to improved mood symptoms.

Diagnostic Interview

Participants underwent a standardized diagnostic interview utilizing the Clinician Administered PTSD Scale (CAPS) to confirm they met criteria for chronic PTSD. The CAPS, widely considered the gold standard in assessing PTSD, is a 30-item structured interview that is based on DSM-IV criteria for PTSD. A CAPS based on DSM-V criteria had yet to be published at the start of the study. The first part of the CAPS asks the participant to describe his traumatic event(s). If there are several combat-related events, the participant was asked to discuss the event that caused him the most distress and discomfort. That event was the primary focus of treatment. Symptoms were assessed based on frequency: (0) *Never*; (1) *Once or twice*; (2) *Once or twice a week*; (3) *Several times a week*; or (4) *Daily or almost every day*, and intensity of the associated distress or discomfort: (0) *None*; (1) *Mild, minimal distress or disruption of activities*; (2)

Moderate, distress clearly present but still manageable, some disruption of activities; (3) *Severe, considerable distress, difficulty dismissing memories, marked disruption of activities*; or (4) *Extreme, incapacitating distress, cannot dismiss memories, unable to continue activities*). The CAPS may be used to assess a current or a lifetime PTSD diagnosis, but for the purposes of this study, current symptomatology (during the past month) was examined. The CAPS was also used to confirm that symptoms have been present for more than one year, and thus that the participant's PTSD was considered chronic. The scale generally takes 45-60 minutes to administer and symptoms are counted as "present" if a frequency of "1 or more" and an intensity of "2 or more" are selected. Severity scores can be calculated by the sum of the frequency and intensity ratings (Blake et al., 1995). This interview was administered prior to the start of treatment, but after the participant had consented.

Psychosocial Questionnaires

SociodemographicCharacteristics. Sociodemographic information was collected at baseline and includes the following characteristics: age, education level, marital status and race. This information was collected prior to the start of treatment.

PTSD Checklist-Military (PCL-M). The PCL-M is a 17-item self-report measure of the 17 DSM-IV symptoms of PTSD. The PCL-M asks about symptoms in response to "stressful military experiences." It is often used with active service members and Veterans and has a variety of purposes, including screening individuals for PTSD, diagnosing PTSD, and monitoring symptom change during and after treatment. It takes approximately 5-10 minutes to complete a PCL-M, which uses a 5-point scale to rate symptom severity over the past week (1 = "not at all; 5 = "extremely"). Evidence

suggests that a 5-10 point change represents reliable change (i.e., change not due to chance) and a 10-20 point change represents clinically significant change (Blanchard, Jones-Alexander, Buckley, & Forneris, 1996).

The test-retest reliability of the PCL-M is above the recommended level of α = .70 after 2–3 days. The original investigation of the PCL-M in Vietnam and Persian Gulf Veterans reported alpha values above .80 (Weathers, Litz, Herman, Huska & Keane, 1993). A later study of female Iraq and Afghanistan Veterans reported alpha values above .75 (Owens, Herrera & Whitesell, 2009). Item-total correlations were more than .40 in Vietnam and Persian Gulf Veterans (Weathers et al., 1993). In terms of convergent validity, the PCL-M had a kappa of .64 with the PTSD section of the SCID in Vietnam Veterans (Weathers et al., 1993). Clinician-rated (CAPS) and PCL-M self-reported symptoms have been shown to be strongly related, *Bs* = 0.95 and 0.80 in the male and female samples, respectively (Lunney, Schnurr & Cook, 2014). No studies were found with the goal of assessing the PCL-M's discriminant validity. This scale was administered prior to treatment, post-treatment, and one week post-treatment.

Treatment Outcome PTSD Scale (TOP-8). The TOP-8 scale was developed as a brief 8-item, clinician-administered scale for use in assessing responses to treatment in patients with post-traumatic stress disorder. It utilizes the eight most commonly reported symptoms of PTSD (Conner & Davidson, 1999). The instrument was developed from a larger post-traumatic stress disorder evaluation scale, the Structured Interview for PTSD (SIP), based on items which occurred frequently in the population and which responded substantially to treatment across time. The measure takes about 5-10 minutes to administer and uses a Likert-type scale to rate the extent to which each symptom has

"troubled the person" during the past week (Conner & Davidson, 1999; Davidson & Colket, 1997).

In a sample of males and females with chronic PTSD, internal consistency of the TOP-8 indicated a Cronbach alpha of 0.73. Test-retest reliability gave a value of r = 0.884 (Connor & Davidson, 1999). In the same sample, convergent validity was strong. For the self-rated Davidson Trauma Scale, the Pearson correlation coefficient was 0.91 ($p < .000$), while for the Impact of Event Scale, the correlation was 0.89 ($p < .000$). The TOP-8 has also been shown to have strong predictive validity. Using positive and negative predictive values (PPV and NPV) and efficiency of the TOP-8, Connor and Davidson (1999) found that the optimum score for rejection of a PTSD diagnosis was 8, at which score the PPV was 0.86, NPV was 1.0, and efficiency was 0.93. For optimal inclusion of patients with a diagnosis of PTSD, a score of 12 was found to be the threshold; at that score, PPV was 1.0, NPV was 0.89, and efficiency was again 0.93. This scale was administered prior to treatment, post-treatment, and one week post-treatment.

Beck Depression Inventory II (BDI-II). The BDI-II is a quantitative measure of depression symptoms and level of severity of those symptoms (Beck, Steer, & Brown, 1996). This is a 21-item instrument with total scores ranging from 0-63. Items are rated on a 0 to 3 rating scale with lower ratings indicating lower severity of symptoms during the past two weeks (verbal anchors are specific to each question). Examples of symptoms assessed are "sadness", with responses ranging from *I do not feel sad* (0) to *I am so sad or unhappy that I cannot stand it* (3), and "loss of pleasure", with responses ranging from *I get as much pleasure as I ever did from the things I enjoy* (0) to *I can't get any pleasure from the things I used to enjoy* (3).

The BDI-II has been found to demonstrate high internal consistency reliability (α = .93 among college students, α = .92 among outpatients; Beck et al., 1996). It has also shown good convergent validity as BDI-II total scores are significantly related to the State-Trait Anxiety Inventory Depression subscale (STAI-D) factor score (r = .76, p < .001; Storch, Roberti, & Roth, 2004) and are more positively correlated with the Symptom Cheklist-90-Revised version (SCL-90-R) Depression subscale (r = .89) than the Anxiety subscale (r = .71) (Steer, Ball, Ranieri, & Beck, 1997). This measure will be administered prior to treatment, post-treatment, and one week post-treatment.

Hamilton Depression Rating Scale (HAM-D). This instrument is used by clinicians to assess the severity of depression in patients already diagnosed with depression and is one of the most commonly used depression rating scales. It is a 17-item instrument that assesses depressed mood, suicide, loss of interest, psycho-motor retardation, agitation, gastro-intestinal symptoms, general somatic symptoms, hypochondriasis, insight, and loss of weight. Items are rated on a scale ranging from three to five options with lower ratings indicating lower severity of symptoms. Scores are obtained by summing the response from each item.

As this instrument measures the clinician's subjective assessment of the patient as opposed to the patient's self-description, it is subject to the biases of the administrator. However, the inter-rater correlations, as reported by the test developer, ranged from 0.84-0.90 (Hamilton, 1960). A more recent meta-analysis carried out with 35 alpha coefficients, obtained from 23 published research studies, showed a mean inter-rater reliability of .79 (SD = 14; Lopez-Piña, Sánchez-Meca & Rosa-Alcázar, 2009). Furthermore, the convergent validity between self-ratings of depression and HAM-D

observer ratings has been found to be very high, with correlations exceeding 0.90 (Bent-Hansen & Bech, 2011). This scale was administered prior to treatment, post-treatment, and one week post-treatment.

Beck Anxiety Inventory (BAI). The BAI is a quantitative measure of anxiety symptoms and level of severity of these symptoms (Beck, Brown, Epstein, & Steer, 1988). This is a 21 item, self-report questionnaire with scores ranging from 0-63. Subjects indicate how much they have been bothered by anxiety symptoms over the past 4 weeks on a 0 (not at all) to 3 (Severely--I could barely stand it) rating scale. Unlike the PCL-M and TOP-8, anxiety symptoms measured by the BAI are not PTSD specific. Rather it is a more generalized anxiety measure.

The BAI has high internal consistency (α =.92) and test-retest reliability over 1 week, r = .75 (Beck et al., 1988). Zero-order correlational analyses have shown support for convergent validity as well. The BAI total and subscale scores were found to be moderately and significantly (Bonferroni's alpha: .05/5 = .01) correlated with other self-report anxiety scales (range, .35 to .69): the A-State, A-Trait, CCL-Anxiety, BSI-Anxiety, and BSI-Somatization subscales (Osman, Kopper, Barrios, Osman & Wade, 1997). This measure will be administered prior to treatment, post-treatment, and one week post-treatment.

Neuropsychological Assessment

All neuropsychological assessments were administered in an order such that verbal tests did not overlap with other verbal tests and visual tests did not overlap with other visual tests. This was to ensure that stimuli from any given assessment did not interfere with performance on any other assessment.

CNS Vital Signs. CNS Vital Signs (CNS-VS) is a compendium of computer-based neurocognitive tests. The psychometric characteristics, including test-retest reliability, concurrent validity, and discriminant validity, of the tests in the CNS-VS battery are reportedly similar to the characteristics of the conventional well-established neuropsychological tests upon which they are. Test-retest reliability (Pearson's *r* for administrations separated by an average of 62 days) for the test components used in the present study ranged from .31 (Stroop Test errors) to .87 (Stroop color-word reaction time). Of the 25 test components examined, only five scores had correlation coefficients lower than 0.6. Reliability coefficients for the five domain scores range from 0.65 to 0.87 (Gaultieri & Johnson, 2006). In terms of convergent validity, moderate correlations were found between CNS-VS tests of memory and executive functioning and traditional neuropsychological tests in these domains. There is no evidence of practice effects according to test developers. Further research indicated that repeated exposure within a 10 day interval did not lead to score improvements in a group of normal controls (Bayan, 2014). However, psychometric properties and potential practice effects of CNS-VS have not been specifically examined in samples of men with PTSD. Cognitive testing will be administered prior to treatment, post-treatment, and one week post-treatment. Testing will include the Verbal Memory Domain, Visual Memory Domain, and Executive Functioning Domain, as these are the most salient for the cognitive issues associated with PTSD.

Verbal Memory Domain. The Verbal Memory Domain test assesses for verbal learning, memory for words, word recognition, and immediate and delayed recall. Fifteen words are presented, one by one, on the screen every two seconds. For immediate

recognition, the participant has to identify those words nested among fifteen new words. Then, after six more tests, there is a delayed recognition trial.

Visual Memory Domain. The Visual Memory Domain test assesses for visual learning, memory for geometric shapes, geometric shapes recognition, and immediate and delayed recall. Fifteen geometric figures are presented, one by one, on the screen. For immediate recognition, the participant has to identify those figures nested among fifteen new figures. Then, after five more tests, there is a delayed recognition trial.

Executive Functioning Domain. The Executive Functioning Domain consists of two tests, the Stroop Test and the Shifting Attention Test**.** The Stroop Test assesses simple reaction time, complex reaction time, inhibition/disinhibition, processing speed, and importantly frontal or executive skills. The test has three parts. In the first part, the words RED, YELLOW, BLUE, and GREEN (printed in black) appear at random on the screen, and the participant presses the space bar as soon as the he sees the word. In the second part, the words RED, YELLOW, BLUE, and GREEN appear on the screen, printed in color. The participant is asked to press the space bar when the color of the word matches what the word says. In the third part, the words RED, YELLOW, BLUE, and GREEN appear on the screen, printed in color. The participant is asked to press the space bar when the color of the word does not match what the word says.

The Shifting Attention Test assesses executive function, shifting sets, rapid decision making with rules and categories, and reaction time. It is essentially a measure of ability to shift from one instruction set to another quickly and accurately. Participants are instructed to match geometric objects either by shape or by color. Three figures appear on the screen, one on top and two on the bottom. The top figure is either a square

or a circle. The bottom figures are a square and a circle. The figures are either red or blue (mixed randomly). The participant is asked to match one of the bottom figures to the top figure. The rules change at random (i.e., match the figures by shape for one trial, and by color for the next).

California Verbal Learning Test Second Edition (CVLT-II). The California Verbal Learning Test (CVLT) is a neuropsychological test that can be used to assess an individual's verbal memory abilities, including immediate free recall, short-delay free recall, short-delay cued recall, long-delay free recall, long-delay cued recall, and long-delay recognition. As such, the CVLT serves as a comprehensive measure of verbal memory in that it incorporated learning and executive memory. For the present study, the long delay free recall score was examined as this is the best measure of verbal memory retrieval. The tester reads aloud a list containing sixteen common words, each of which belongs to one of four categories: there are four pieces of furniture, four vegetable, four ways of traveling, and four animals. The participant is then asked to recall as many of these items as possible. First, the tester records how many items the subject remembers over several repeated trials, which tests the participant's learning curve. Next, the tester gives a second list to see if the participant is able to keep the items from each list separate, or if the two lists become confused. Finally, there is a delay of 20 minutes, and then the tester again asks the participant to recall the initial list of words; this is the measure examined in the present study. Because it measures several aspects of memory and learning, the CVLT is popular as a neuropsychological test (Delis, Kramer, Kaplan, & Ober, 2000).

In a study evaluating 1-month test-retest reliability and practice effects associated with the CVLT-II, results revealed generally large test-retest correlation coefficients for the primary CVLT-II measures (range = 0.80–0.84). Reliable change indices were also generated and applied to primary CVLT-II variables to determine the base rates of significant improvements (range = 2–10%), declines (range = 0–7%), and stability (range = 85–97%) in performance over time, supporting low potential for practice effects given that is probable 85-97% of those tested will maintain a stable performance over time (Woods, Delis, Scott, Kramer & Holdnack, 2006). However, it is again worth noting that psychometric properties and potential practice effects of the CVLT-II have not been specifically examined in samples of men with PTSD, which is a limiting factor for the present study. The CVLT takes approximately 35 minutes to administer and was given prior to treatment, post-treatment and one week post-treatment.

Rey Complex Figure Test (RCFT). Results of factor analysis suggest that the RCFT captures five domains of neuropsychological functioning: visuospatial recall memory, visuospatial recognition memory, response bias, processing speed, and visuospatial constructional ability (Meyers & Meyers, 1995). For the present study, visuospatial recall was the measure examined as it is the best indicator of visual memory retrieval. The RCFT serves as a more comprehensive measure of visual memory as it incorporates executive memory in that visual stimuli have to be recalled *and* arranged in a specific configuration. Participants are first asked to copy a complex line drawing, and are subsequently asked to recall as much of the drawing as they can after a 3-minute delay, and then after a 30-minute delay. The recognition trial asks participants to select

designs that were part of the initial figure from 24 designs, some of which were part of the initial figure and some of which were not (Meyers & Meyers, 1995).

Numerous studies have found the RCFT to have good interrater reliability for all trials, including the delayed recall trial used in the present study, ($r = 0.92$ $p < 0.0001$, Luzzi et al., 2011; ($r = .98$, $df = 85$, $p < .001$, Loring, Martin, Meador & Lee, 1990; $r = .96$, $p < .001$, Berry , Allen & Schmitt, 2007), which is of great importance for this measure as there is a subjective element to the scoring. Moderate test-retest reliability has been observed for the delayed recall condition ($r = .59$, $p < .001$, Berry et al., 2007). Validity investigations have focused primarily on the RCFT's ability to detect deficits of visuo-spatial memory, thought to result from lesions of the right temporal lobe (Milner, 1975). Binder (1982) found that right hemisphere stroke patients scored significantly below left hemisphere patients on RCFT recall, suggesting the measure is sensitive to visuo-spatial memory deficits rather than general memory deficits. With regard to the RCFT as a general memory assessment, it has been found that, for patients matched on demographic characteristics, RCFT scores are significantly lower for Alzheimer's patients than for controls (Berry et al., 2007). In terms of practice effects, Levine, Miller, Becker, Selenes and Cohen (2004) found a mean increase of 2.3 points at re-assessment, with the mean time interval being 251 days. The sample consisted of 478 healthy men. While the increase in score was minimal, the time interval was significantly longer than in the present study. Once again, it is also important to mention that psychometric properties and potential practice effects of the RCFT have not been specifically examined in samples of men with PTSD. The RCFT takes approximately 35 minutes to administer and was administered prior to treatment, post-treatment and one week post-treatment.

Wisconsin Card Sorting Test (WCST). The WCST was developed to assess abstract reasoning and ability to shift cognitive strategies in response to environmental changes. Unlike other tests of abstraction, the WCST provides objective measures not only of overall ability, but also of particular sources of difficulty--e.g., inefficient initial conceptualization, perseveration, failure to maintain set, and inefficient learning across several stages of the test. The test uses stimulus and response cards that show various forms in various colors and numbers. It requires the participant to sort the cards according to different principles (i.e., by color, form, or number). As the test progresses, there are unannounced shifts in the sorting principle which require the participant to alter his approach.

The developers of the test report generalizability coefficients of .37 to .72 for the various measures of the test (Heaton, 1993). Test-retest reliability findings are mixed, with the test proving much more reliable in clinical samples with initial scores that are below average than in those with average or above average initial scores (Strauss, Sherman & Spreen, 2006). Average correlations on test measures administered a median of 12 days apart was .64 in a sample of patients with broadly average scores at first administration (Ingram, Greve, Ingram & Soukup, 1999). The literature is also mixed on practice effects for the WCST. Basso, Bornstein and Lang (1999) calculated reliable change indices using the standard error of prediction to estimate the range of change in scores over a 12 month period that might be expected while accounting for measurement error and practice effects. They found a fairly wide range of retest scores that may fall within a 90% confidence interval and still reflect measurement error rather than meaningful change. However, Tate, Perdices and Maggiotto (1998) reported generally

strong stability coefficients in the context of no significant change in performance over time in normal individuals. Again, it is important to mention that psychometric properties and potential practice effects of the WCST have not been specifically examined in samples of men with PTSD. Thus, results on neurocognitive measures in the present study must be interpreted with caution. There is considerable shared variance between the WCST and other tests of executive functioning, particularly tests of conceptual reasoning, but research also demonstrates that different executive functioning tests measure different abilities within conceptual reasoning. For instance, Perrine (1993) found the WCST to share 30% variance with the Category Test, which is substantial, but it is clear they are measuring separate factors to some extent. Perrine observed that unlike the Category Test, the WCST is not merely a concept identification test, but also an attribute identification test. Numerous studies have found, through factor analysis, that the WCST is primarily a measure of shifting ability, supporting the commonly held view that the WCST is an executive task (Fisk & Sharp, 2004; Miyake, Emerson & Friedman, 1999, Miyake et al., 2000). Thus, it seems WCST is a test of one or possibly a few very important aspects of executive functioning, but not "executive functioning" as a whole. It seems unlikely that a single measure could assess all of executive functioning as it encompasses such a myriad of abilities, but the CNSVS Executive Functioning Domain score is more general than most because it is derived from several tests measuring different aspects of executive functioning. The test takes approximately 30 minutes to administer (Nelson, 1976). This test was administered prior to treatment, post-treatment and one week post-treatment.

Aparatus

The Neuronetics NeuroStar Transcranial Magnetic Stimulation (TMS) System (Model Number 81-00315-000; Serial Number 0276) was used in the clinical procedures. It is a Class II medical device that produces pulsed magnetic fields of short duration. These rapidly alternating magnetic fields induce electrical currents within targeted regions of the cortex associated with physiological and functional brain changes (Horvath, Mathews, Demitrack, & Pascual-Leone, 2012).

Clinical Procedures

TMS Treatment. For the present study, participants received 16 sessions (one 1-hour session per day) of low frequency (1Hz) TMS over a 5 week period; 1session per day for 10 consecutive days, excluding weekends, and the remaining 6 sessions as a 3 week taper (three in week 3, two in week 4, and one in week 5). Table 1 details the timing and clinical procedures of the protocol. The Neurostar coil was first positioned above the right DLPFC (generally thought to be approximately 5cm anterior to an individual's pre-central gyrus or motor strip), then repositioned to the supplementary motor area for the remaining half of the treatment. During the treatment, the coil was held in place on the skull; it discharged its magnetic field at a rate, frequency and duration that was specific to each patient and his prescribed treatment. Because the magnetic field is extremely focused – generally penetrating no more than 2-3 cm of cortex, the induced electrical current is also highly specific in terms of location.

The treatment protocol included the following parameters: 2400 pulses/session (1200 pulses above the right DLPFC and 1200 at the supplementary motor area), 1 pulse per second at 110% of the Motor Threshold (MT) intensity for the right DLPFC and 100% for the supplementary motor area. The initial treatment session involved the

determination of a patient's motor threshold (the lowest amount of stimulation required to produce a consistent motor response). This step allowed for the treatment to be tailored to each individual thus avoiding over- or under-stimulating. MT differences between individuals are related to age, gender and cortical excitability, among other factors (Lisanby, Kinnunen, & Crupian, 2002; Wassermann, 1996). Each TMS treatment lasted for 40 minutes, with each brain area treated for 20 minutes.

Imaginal Exposure Treatment. Prolonged imaginal exposure was administered while the participants were seated in the apparatus, concurrently with TMS treatment. After each TMS/exposure session was finished, an additional 20 minutes was spent processing the patient's reactions to the prolonged exposure. Thus, each session was approximately one hour. The protocol for imaginal exposure followed the current PTSD guidelines for Prolonged Exposure Therapy (VA, 2009), but did not include the "at home" portion of the treatment as that would be difficult to standardize. The standardized dialogue for the imaginal exposure procedure was adapted from Edna Foa's protocol for treating PTSD with exposure (Foa et al., 2007). The goal of this therapy is to emphasize repetitive expression of traumatic memories to facilitate five primary goals (Foa, 2007; Ruzek et al., 2002). According to Foa et al. (2007) and the Veterans Administration (2009), first, repeatedly recalling the memory will help the participant to organize the memory and get new perspective about what happened during and after the trauma. Second, repeated revisiting of the trauma helps the participant to differentiate between "remembering" the traumatic event and "being re-traumatized." Third, repeated imaginal exposure to the trauma memory for an extended period of time lowers anxiety through habituation. Fourth, repeatedly revisiting the memory in imagination promotes

differentiation between the event and similar events and thereby decreases the generalization of fear from the specific trauma to similar but safe situations. Fifth, repeatedly recounting the memory enhances the participant's sense of self-control and personal competence. The participant feels progressively better about himself as he stops avoiding and masters his fears. The therapy consists of three parts, each introduced separately over the course of treatment: education, breathing, and talking through the trauma.

The participants were educated about TMS to understand the goals of the treatment in relation to their symptoms. This provided a foundation for the next sessions. As per Foa et al.'s (2007) protocol, the second part of therapy consisted of breathing skills to aid the participant in learning how to relax in order to manage immediate stress. Finally, the imaginal exposure procedure was used to guide participants in talking through their traumatic event. The traumatic event addressed was determined during the CAPS, as described above. Again, the goal of this part of the therapy was to help the participant reduce negative thoughts and perceptions of danger associated with the trauma and increase perceived self-control of memories. During the TMS treatment sessions, the clinician encouraged the participants to express the trauma they experienced though imaginal exposure. Following TMS, the imaginal exposure session was processed according to Prolonged Exposure guidelines (Foa et al., 2007).

Table 1

Timing and Clinical Procedures of the Protocol

Pre-Tx	**Session 1**	**Sessions 2-10**	**Sessions 11-15**	**Session 16**	**1 Week Post Tx**
CAPS	MT Determination	Daily TMS for 2 weeks	TMS Taper over 3 weeks	Final TMS Session	Psychosocial Assessments
Psycho-education	1st TMS Tx	PE concurrent with TMS	PE concurrent with TMS	Psychosocial Assessments	Cognitive Assessments
Breathing Retraining				Cognitive Assessments	
Psychosocial Assessments					
Cognitive Assessments					

Design and Data Analyses

In the present study, change was assessed over time for the same group of participants in a repeated measures observational design. The form of the design is A (baseline), B (measures taken post-treatment, the day of the last session), A (removal of treatment one week post), with "A" representing the control condition, and "B" representing the treatment condition. The design was chosen for several reasons, including limited funding, which necessitates a limited number of participants, but also because a small pilot study is warranted to determine if the proposed treatment is viable, prior to a larger RCT.

This repeated measures design reduces the variance of estimates of treatment-effects, allowing statistical inference to be made with a small sample size. A power analysis using G*Power 3.1indicated that a minimum of 5 participants are needed to obtain a significant result for PTSD symptom change following TMS, with a large effect size. Effect size inputs were from Berlim and Van den Eynde's (2012) meta-analysis of studies using TMS to the DLPFC for treatment of PTSD. They found large effect sizes for active TMS (versus sham) for self-reported PTSD symptoms (Hedge's g = 1.91), depression symptoms (Hedge's g = 0.85) and anxiety symptoms (Hedge's g = 1.24). Although effect size inputs for depression and non-PTSD specific anxiety were quite large, they were marginally smaller than the effect size input for PTSD symptoms. Accordingly, the power analyses did indicate that this study may be underpowered to detect change in depression and non-PTSD anxiety symptoms. A further power analysis indicated that a minimum of 4 participants are needed to detect changes in executive functioning following TMS to the DLPFC. Effect size inputs were from Bayan's (2014)

study examining cognitive changes following TMS in a depressed sample. Executive functioning was measured using CNS-VS with an effect size of $\eta^2_p = 0.781$. While effect sizes for change in executive functioning in a sample with PTSD would be most appropriate, this was not found in the literature. As such, it may be that the present study is underpowered to detect such effects. There were no articles found examining changes in verbal and visual memory following TMS to the DLPFC and/or the SMA, in a sample with PTSD. As such, effect sizes were calculated from Martis et al.'s (2003) means and standard deviations in their study examining changes in verbal and visual memory following TMS to the DLPFC in a depressed sample. Effect size inputs were *Cohen's d* = 0.38 for delayed visual memory and *Cohen's d* = 0.73 for delayed verbal memory. Power analyses indicated that the present study may be underpowered to detect changes in verbal and visual memory post-TMS. Further, as inputs for power analyses of cognitive measures are from a TMS treatment sample with depression rather than with PTSD, all statistical results must be interpreted with caution. When a study is underpowered, this can result in higher likelihood of Type II error, or failing to detect an effect when it is present. An underpowered study can also result in a larger variance of the estimates of the parameter being estimated. In other words, the sampling distribution of sample means is wide. This reflects the general phenomenon that studies with low power have a higher chance of a large effect size than studies with high power. In particular, when there is a Type I error (falsely rejecting the null hypothesis), the effect will appear to be stronger with a small sample size (lower power) than with a large sample size (higher power). This may suggest an effect that is not there. As such, results of clinical significance will be granted more weight than results of statistical significance.

This design was further chosen for the sake of efficiency, as it allows the study to be completed more quickly. Finally, this design was chosen for its longitudinal analysis. Repeated measures designs allow one to monitor how participants change over time, which is certainly relevant as client change over time is the foundation of clinical work. This design does however have some limitations due to its not being a randomized controlled trial, such as the possibility of maturation; influence of events outside the experiment that may change responses between measures; the risk of order effects, such as practice, boredom, or fatigue; the risk of expectancy bias. There is also the risk of unintended treatment provider influence (e.g., rapport between patient and treatment provider may be stronger in the present study than in the current standard of care due to treatment being provided every day as opposed to once or twice a week).

Descriptive statistics (percentages, means, and standard deviations) were used to describe patient characteristics (e.g., age, education level, race, and marital status). To measure efficacy of TMS, repeated measures ANOVAs were used to examine changes in PTSD symptoms, depression symptoms, anxiety symptoms, and cognitive functioning to TMS treatments over time. Although the sample size is quite small, this does not violate the assumptions of an ANOVA, as minimum sample size for a one-way ANOVA F-test is one more than the number of groups (Boos & Hughs-Oliver, 2000; Bradley, 1980). However, with a sample size of seven, a visual plot is likely too scarce to prove a normal distribution. Thus, results of the ANOVAs should be interpreted with caution. The omnibus ANOVAs were followed by simple contrast post hoc comparisons to compare within-subjects factor - time points to respective baseline measures. In previous studies treating PTSD with TMS to the right DLPFC, decreases in PTSD symptoms ranged from

a 29.3% decrease to a 36.9% decrease when measuring symptoms with the PCL (Boggio et al., 2010; Cohen et al., 2004). The hope is to replicate or improve upon these results as this study has a similar sample size and a somewhat similar protocol to said studies, but with the addition of prolonged exposure treatment. Again, as mentioned above, comparisons across studies are merely speculative and not meant as a substitute for a control group in the present study. Additionally, a 5-10 point decrease on the PCL is typically considered statistically significant, while a 10-20 point decrease is considered clinically significant (Blanchard et al., 1996). For all other measures used, a change in 1 standard deviation would indicate clinical benefit.

CHAPTER 3

RESULTS

Sample Demographics

In order to characterize the sample, descriptive statistics were conducted. Seven total patients completed a course of combined imaginal exposure and TMS for chronic, treatment-resistant PTSD. As seen in Table 2, the total mean age of the 7 patients was 39.29 with a standard deviation of 6.45. The sample was comprised of male OEF/OIF combat Veterans of Caucasian (n = 5), African American (n = 1) and Bi-racial (n = 1) background. Patient education level fell between a high school degree and a master's degree with 57% of the sample (n = 4) completing some college but no college degree. All patients met DSM-IV criteria for chronic Post Traumatic Stress Disorder as per the CAPS interview.

Table 2

Demographic Data

	Min	*Max*	$\bar{x}$	*SD*
Age	31	47	39.29	6.45

	n	*%*
Gender		
Male	7	100.0
Ethnicity		
Caucasian	5	71.4
African American	1	14.3
Bi-racial	1	14.3
Marital Status		
Married	3	42.9
Divorced	3	42.9
Separated	1	14.3
Single	0	0
Highest Education		
HS Diploma	1	14.3
Some College	4	57.1
Associate's Degree	0	0
Bachelor's Degree	1	14.3
Master's Degree	1	14.3
Total	7	

Total scores on measures of PTSD symptom severity, depression symptom severity and anxiety symptom severity, as well as total scores on neurocognitive measures of executive functioning, verbal memory and visual memory were collected at pre-treatment, immediately post-treatment (same day) and one week post-treatment. Scores at these three time points were then compared using repeated measures omnibus ANOVAs followed by post-hoc analyses. Clinical significance was also calculated to help determine the practical importance of the treatment effects.

Research Question 1

Is low-frequency TMS to the right DLPFC and the SMA combined with prolonged imaginal exposure associated with reduced PTSD symptoms and concomitant mood and anxiety symptoms (using the following scales: The PTSD Checklist-Military [PCL-M], the Treatment Outcome PTSD Scale [TOP-8], the Beck Depression Inventory II [BDI-II], the Hamilton Depression Rating Scale [HAM-D], and the Beck Anxiety Inventory [BAI]) after 16 treatment sessions? If symptoms are reduced, are reductions maintained at one week post-treatment?

Five independent repeated measures ANOVAs were conducted to compare mean total score differences for PTSD symptoms and associated mood and anxiety symptoms (using the total scores for the PCL-M and TOP-8 to measure PTSD symptom severity; the BDI-II and HAM-D to measure depressive symptom severity; and the BAI to measure general anxiety symptom severity) from pre-treatment to post-treatment and one week post-treatment. The one-way repeated measures ANOVA comparing total mean scores on the PCL-M at each time point revealed statistically significant differences across test administrations, $F(2,12) = 15.49$, $p < .001$, $\eta^2_p = 0.721$, 90% CI [0.354,

0.806][4]. Tukey's HSD post-hoc analyses further revealed that both the post-treatment PCL-M total mean score (38.71 ± 13.91) and the one week post-treatment mean score (33.29 ± 16.62) were significantly lower (reduced PTSD symptom severity) than the pre-treatment mean score (64.71 ± 12.62; $p < .05$). While there was a further slight reduction in mean score from post-treatment to one week post-treatment, this was not statistically significant. Thus, in terms of PTSD symptom severity as measured by the PCL-M, statistically significant reductions were found after 16 sessions of treatment, with those reductions remaining stable at one week post-treatment (Figure 1). This represents a 51.4% decrease in PTSD symptoms. Notably, clinically significant reductions were also found. All patients demonstrated clinically significant reductions (more than 10-point change) in PTSD symptoms from pre-treatment to post-treatment on the PCL-M, with 86% of the sample falling below the 50-point cutoff score for likely a PTSD diagnosis by one week post-treatment.

Similarly, the second one-way repeated measures ANOVA showed a significant decrease in TOP-8 mean total scores across test administrations, $F(2,12) = 16.03$, $p < .001$, $\eta^2_p = 0.728$, 90% CI [0.366, 0.811]. Tukey's HSD post-hoc analyses again revealed that both the post-treatment mean score (11.57 ± 6.21) and the one week post-treatment mean score (11.14 ± 8.84) were significantly lower (reduced PTSD symptom severity) than the pre- treatment mean score (24.00 ± 5.23; $p < .05$). Once again, there was a slight reduction in mean score from post-treatment to one week post-treatment, but this was not statistically significant. And so, in terms of PTSD symptoms as measured by the TOP-8,

[4] A 90% rather than 95% confidence interval was used for η^2_p for the following reason: While a 95% CI is traditionally reported with *Cohen's d*, *Cohen's d* can be both positive and negative. η^2 is squared, and can therefore only be positive. If a 95% CI is calculated, it may result in situations where the confidence interval includes values less than 0. Furthermore, a 95% CI around *Cohen's d* equals a 90% CI around η^2 for exactly the same test, (Steigler, 2004).

significant reductions were found after 16 sessions of treatment, with those reductions remaining stable at one week post-treatment (Figure 2).

The third and fourth one-way repeated measures ANOVAs comparing pre-treatment, post-treatment and one week post-treatment mean scores for severity of depressive symptoms determined a significant decrease in BDI-II mean total scores, $F(2,12) = 20.56$, $p < .001$, $\eta^2_p = 0.774$, 90% CI [0.452, 0.843] and in HAM-D mean total scores, $F(2,12) = 25.92$, $p < .001$, $\eta^2_p = 0.812$, 90% CI [0.529, 0.869]. Tukey's HSD post-hoc analyses revealed that both the post-treatment mean score (12.57 ± 10.31) and the one week post-treatment mean score (8.57 ± 8.83) for the BDI-II were significantly lower (reduced depressive symptom severity) than the pre- treatment mean score (33.29 ± 8.79; $p < .05$). While there was a further reduction in mean score from post-treatment to one week post-treatment, this was not statistically significant. In terms of clinical significance, 100% of the sample demonstrated clinically significant reductions (as measured by 1 SD in change from the pre-treatment measure) in depressive symptoms from pre-treatment to post-treatment on the BDI-II. At pre-treatment 57% of patients had severe levels of depressive symptoms as per the BDI-II and the remaining 43% had moderate levels of depressive symptoms. By one week post-treatment, 14% of the sample had moderate levels of depressive symptoms, with 86% of the sample falling below the 14-point cutoff score for mild levels of depressive symptoms.

The same pattern emerged with Tukey's post-hoc analyses of the HAM-D mean total scores, with both the post-treatment mean score (9.43 ± 5.29) and the one week post-treatment mean score (7.57 ± 4.61) being significantly lower (reduced depressive symptom severity) than the pre-treatment mean score (24.00 ± 5.23; $p < .05$). Again,

while there was a further reduction in mean score from post-treatment to one week post-treatment, this was not statistically significant. Thus, in terms of depressive symptom severity as measured by the BDI-II and the HAM-D, significant reductions were found after 16 sessions of treatment, with those reductions remaining stable at one week post-treatment (Figures 3 and 4).

Finally, prior to the fifth one-way repeated measures ANOVA of mean total BAI scores, winsoration[5] was required for the one week post-treatment data to eliminate a major outlier that was skewing the data. A calculation of the interquartile range was used to determine that one value for the BAI post-treatment measure was beyond the outer fence of the upper quartile, and thus was a major outlier. As this value was such an extreme outlier, and as the patient who reported this value experienced a significant adverse personal event between his post-treatment BAI score (25 points) and his one week post-treatment BAI score (47 points), his one week post-treatment score was winsorized to bring it back into range with the other one week post-treatment scores.

Following winsorization of the data, a one-way repeated measures ANOVA showed a significant decrease in anxiety symptom severity as measured by BAI mean total scores across test administrations, $F(2,12) = 7.71$, $p = .007$, $\eta^2_p = 0.562$, 90% CI [0.135, 0.697][6]. Tukey's HSD post-hoc analyses further revealed that both the post-treatment mean score (11.71 ± 8.83) and the one week post-treatment mean score (7.29 ±

[5] Winsorising is a commonly used transformation of statistics that limits extreme values in the data to reduce the effect of possibly spurious outliers.

[6] Prior to winsoration, the omnibus ANOVA for BAI mean total scores did not show a significant decrease in anxiety symptom severity across test administrations, $F(2,12) = 3.56$, $p = .061$, $\eta^2_p = 0.372$. However, a one-way repeated measures ANOVA comparing only pre- and post-treatment mean total scores revealed a significant decrease in mean total BAI scores form pre- to post-treatment, $F(1,6) = 6.73$, $p < .05$, $\eta^2_p = .529$, thus indicating that the outlier in the one week post-treatment measure was likely skewing the results of the omnibus ANOVA.

5.02) were significantly lower (reduced anxiety) than the pre- treatment mean score (25.57 ± 14.93; $p < .05$). While there was a further slight reduction in mean score from post-treatment to one week post-treatment, this was not statistically significant. Thus, in terms of non-PTSD specific anxiety symptom severity as measured by the BAI, significant reductions were found after 16 sessions of treatment, with those reductions remaining stable at one week post-treatment (Figure 5). With regard to clinical significance, 43% of the sample demonstrated clinically significant reductions (as measured by 1 SD in change from the pre-treatment measure) in anxiety symptoms from pre-treatment to post-treatment on the BAI. Means, standard deviations and confidence intervals for PCL-M, TOP-8, BDI-II, HAM-D and BAI pre-treatment, post-treatment and one week post-treatment scores are reported in Table 3.

Table 3

Mean Total Scores, Standard Deviations (SD) and 95% Confidence Intervals [95% CI] at Pre-Treatment, Post-Treatment and One Week Post-Treatment for PTSD, Depression and Anxiety Symptoms

	Pre-Treatment Mean (SD) [95% CI]	Post-Treatment Mean (SD) [95% CI]	One Week Post Mean (SD) [95% CI]
PTSD Symptoms			
PCL-M	64.71 (12.62) [53.04, 76.39]	38.71 (13.91) [25.85, 51.58]	33.29 (16.62) [17.91, 48.66]
TOP-8	24.00 (5.23) [19.17, 28.84]	11.57 (6.21) [5.82, 17.32]	11.14 (8.84) [2.97, 19.32]
Depression Symptoms			
BDI-II	33.29 (8.79) [25.16, 41.41]	12.75 (10.31) [3.04, 22.11]	8.57 (8.83) [0.41, 16.74]
HAM-D	25.14 (7.97) [17.77, 32.51]	9.43 (5.29) [4.54, 14.32]	7.57 (4.61) [3.31, 11.84]
Anxiety Symptoms			
BAI	25.57 (14.93) [11.76, 39.38]	11.71(8.83) [3.55, 19.38]	7.29 (5.02) [2.64, 11.93]

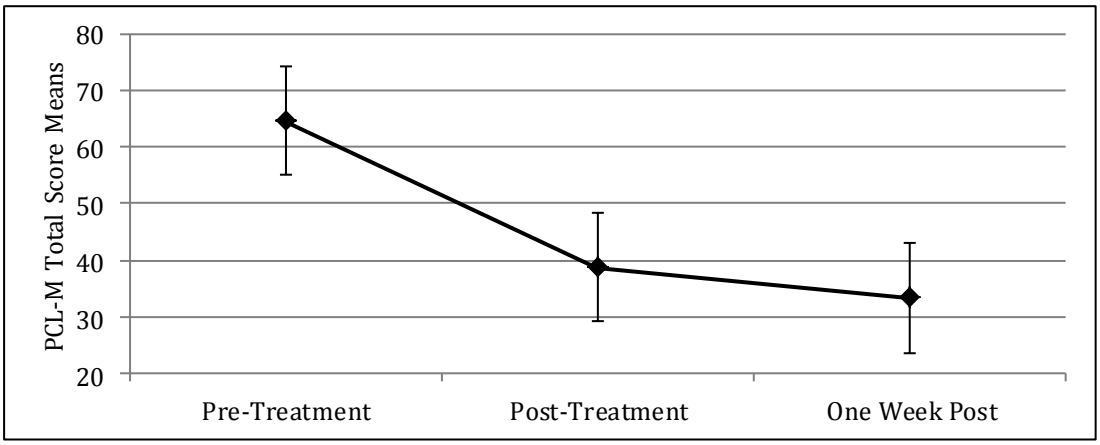

Figure 1. PCL-M 3-Time Point Total Score Means

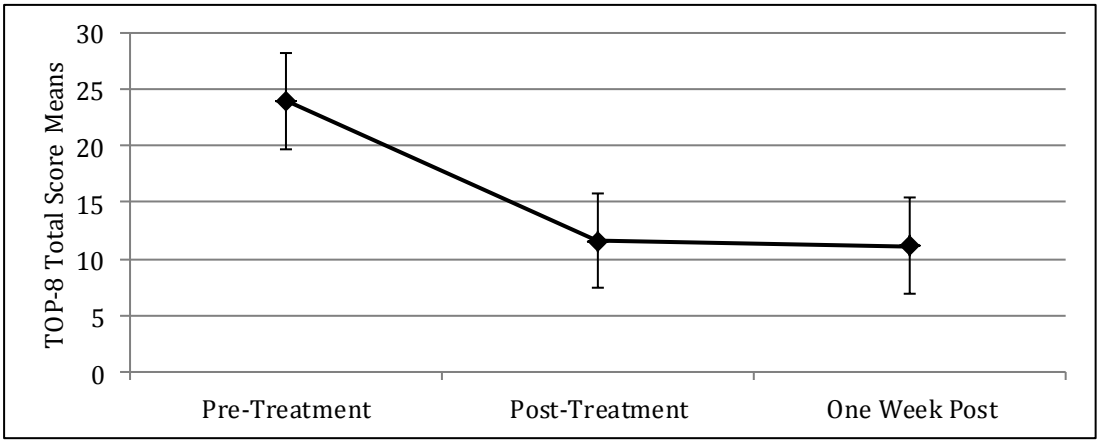

Figure 2. TOP-8 3-Time Point Total Score Means

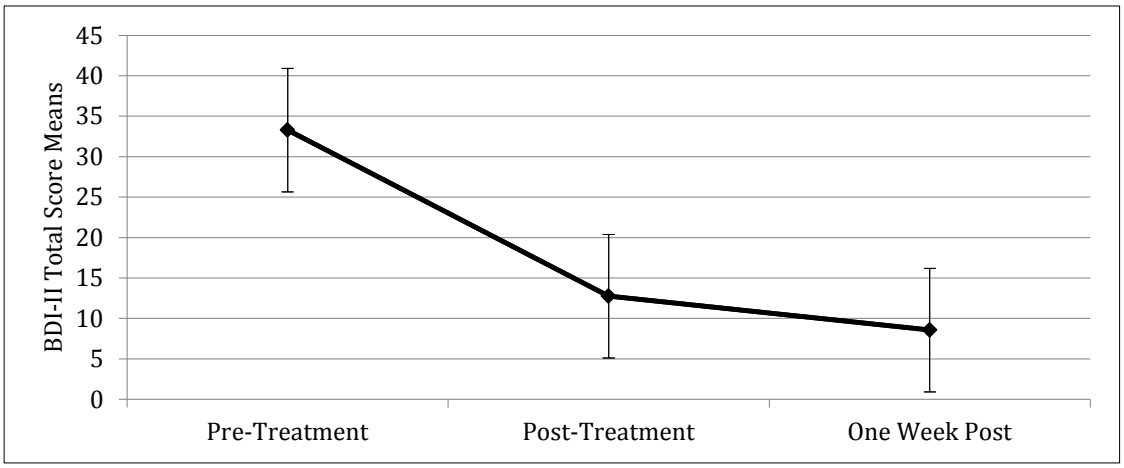

Figure 3. BDI-II 3-Time Point Total Score Means

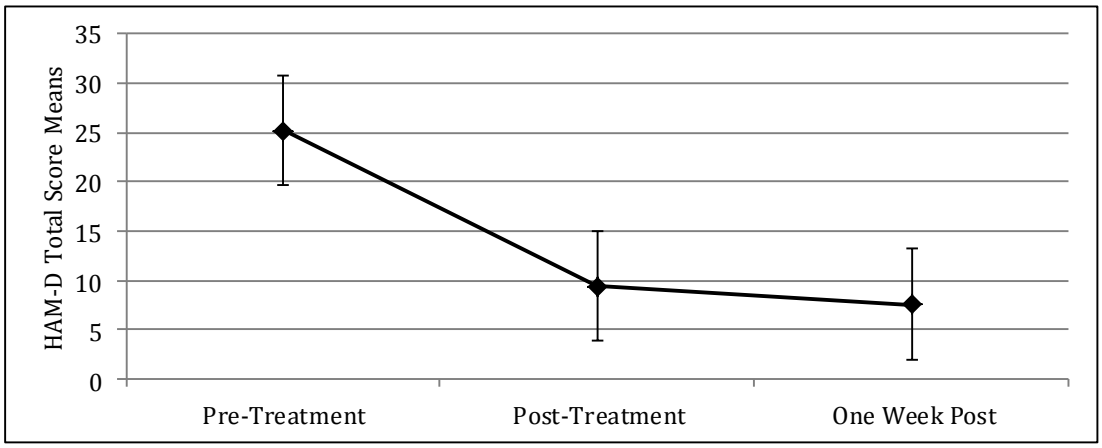

Figure 4. HAM-D 3-Time Point Total Score Means

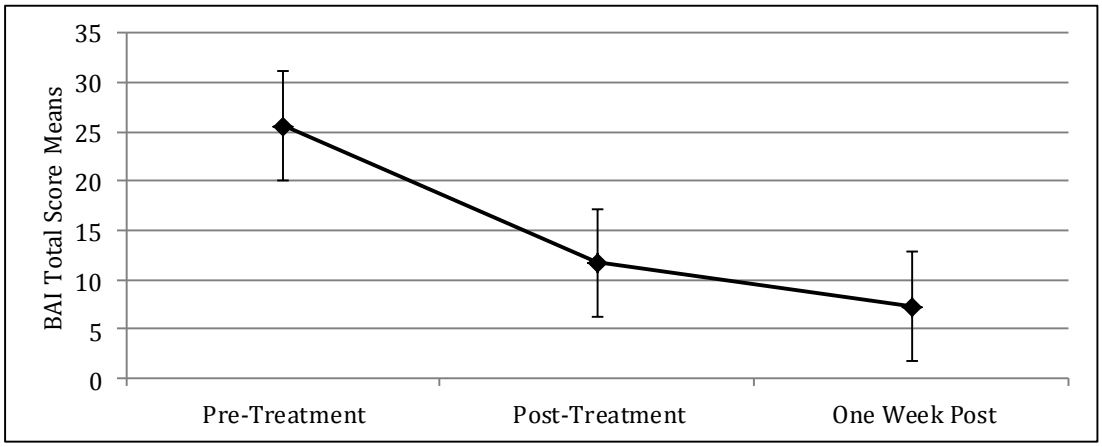

Figure 5. BAI 3-Time Point Total Score Means

Research Question 2

Is low-frequency TMS to the right DLPFC and SMA combined with prolonged imaginal exposure associated with improved neurocognitive functioning, including executive functioning, verbal memory and visual memory (using the following scales: CNS Vital Signs [CNS-VS], the California Verbal Learning Test-Second Edition [CVLT-II], the Rey Complex Figure Test [RCFT], and the Wisconsin Card Sorting Test [WCST]) after 16 treatment sessions? If improved cognitive functioning is observed, are gains maintained one week post-treatment?

Prior to carrying out the analyses for research question 2, correlations and Chi-square analyses were conducted to assess for any appropriate covariates to be included in the repeated measures ANOVA analyses. In order to be excluded from the analyses, variables must covary with treatment measures across all three time points. Kendall's Tau-b correlations[7] were conducted between potential covariates and each cognitive test (CNS-VS Indices, CVLT-II, RCFT, and WCST) at each time point (pre-treatment, post-treatment, and 1 week post-treatment). Bi-serial correlations were conducted for all continuous variables (e.g., age, baseline PCL-M score, baseline TOP-8 score, baseline BDI-II score, baseline HAM-D score, and baseline BAI score), while categorical and ordinal variables (e.g., race and education level) were tested using Chi-square analyses. Results identified no significant covariates across all three time points for any of the neurocognitive measures As no variables covaried significantly with treatment measures

[7] Kendall's tau-b correlations were chosen as they are the most conservative and resilient to the effects of a small sample size. Although, even Kendall's tau is most stable with a sample size of at least 10. As such, correlations should be interpreted with caution due to possible instability. For a sample size of 7, the critical value of *tau* for $\alpha = .05$ is .6190 (Abdi, 2007).

across all three time points, their variance was not excluded from the analyses. Correlations are listed in Tables 6 and 7 in the Appendix.

Research question 2 examines whether a course of TMS administered concurrently with prolonged imaginal exposure for the treatment of PTSD is associated with changes in neurocognitive scores by end of treatment. CNS-VS was used to assess cognition at pre-treatment, post-treatment and one week post-treatment. Additionally, more traditional, well-established neuropsychological tests were used to examine the domains of executive functioning (WCST) and memory (CVLT-II and RCFT) as research indicates PTSD-associated deficits in these domains (Uddo et al., 1993; Polak et al., 2012).

Three independent repeated measures ANOVAs were conducted to compare standard mean score differences for three CNS-VS cognitive domains (Executive Functioning, Verbal Memory and Visual Memory) for pre-treatment, post-treatment and one week post-treatment time-points. The one-way repeated measures ANOVA for Executive Functioning Domain standard scores revealed statistically significant differences across test administrations, $F(2,12) = 4.79$, $p < .05$, $\eta^2_p = .444$, 90% CI [0.032, 0.612]. Tukey's HSD post-hoc analyses revealed that the post-treatment mean score (91.29 ± 34.35) was not significantly higher than the pre-treatment mean score (71.57 ± 31.80). However, the one week post-treatment mean score (98.57 ± 35.41) was significantly higher than the pre-treatment mean score ($p < .05$). While there was a slight improvement in performance from post-treatment to one week post-treatment, this difference was not statistically significant. Thus, in terms of executive functioning as measured by CNS-VS, significant improvement was observed, but not until one week

post-treatment (Figure 6).

One-way repeated measures ANOVAs examining the CNS Vital Signs Verbal Memory and Visual Memory Domains revealed no statistically significant differences across test administrations for either verbal memory, $F(2,12) = 0.52$ $p = .607$, $\eta^2_p = .080$, 90% CI [0.000, 0.266] or visual memory, $F(2,12) = 0.05$ $p = .947$, $\eta^2_p = .009$, 90% CI [0.000, 0.101] (Figures 7 and 8). Means, standard deviations and confidence intervals for CNS-VS Executive Functioning Domain, Verbal Memory Domain and Visual Memory Domain standard scores at pre-treatment, post-treatment and one week post-treatment scores are reported in Table 4.

Three additional independent repeated measures ANOVAs were conducted to compare mean score differences for executive functioning (WCST), verbal memory (CVLT-II) and visual memory (RCFT) for pre-treatment, post-treatment and one week post-treatment time-points. These additional assessments were used as more, well-established measures of the aforementioned cognitive domains. The one-way repeated measures ANOVA of the WCST Total Conceptual Level Responses scores revealed no statistically significant differences across test administrations, $F(2,12) = 0.30$, $p = .749$, $\eta^2_p = .047$, 90% CI [0.000, 0.204]. Thus, in terms of executive functioning as measured by the WCST, significant improvement was not observed (Figure 9).

The one-way repeated measures ANOVA for CVLT-II long delay free recall scores revealed statistically significant differences across test administrations, $F(2,12) = 9.04$, $p < .005$, $\eta^2_p = 0.601$, 90% CI [0.179, 0.724]. Tukey's HSD post-hoc analyses revealed that the post-treatment mean score (10.57 ± 4.16) was not significantly higher than the pre-treatment mean score (8.57 ± 3.36). However, the one week post-treatment

mean score (12.71 ± 3.99) was significantly higher than the pre-treatment mean score ($p < .05$). While there was an improvement in performance from post-treatment to one week post-treatment, this was not statistically significant. Thus, in terms of verbal memory as measured by the CVLT-II, significant improvement was observed, but not until one week post-treatment (Figure 10).

The one-way repeated measures ANOVA for RCFT delayed recall scores revealed statistically significant differences across test administrations, $F(2,12) = 13.44$, $p < .001$, $\eta^2_p = .691$, 90% CI [0.306, 0.786]. Tukey's HSD post-hoc analyses revealed that the post-treatment mean score (24.29 ± 9.03) was significantly higher than the pre-treatment mean score (18.79 ± 6.40). The one week post-treatment mean score (27.93 ± 8.61) was also significantly higher than the pre-treatment mean score ($p < .05$). While there was an improvement in performance from post-treatment to one week post-treatment, this was not statistically significant. Thus, in terms of visual memory as measured by the RCFT, significant improvement was observed at post-treatment and maintained at one week post-treatment (Figure 11). Means, standard deviations and confidence intervals for WCST, CVLT-II and RCFT scores at pre-treatment, post-treatment and one week post-treatment scores are reported in Table 4.

Table 4

Mean Scores, Standard Deviations (SD) and 95% Confidence Intervals [95% CI] at Pre-Treatment, Post-Treatment and One Week Post-Treatment for CNS-VS Executive Functioning, Verbal Memory and Visual Memory Domains, and WCST, CVLT-II and RCFT

	Pre-Treatment Mean (SD) [95% CI]	Post-Treatment Mean (SD) [95% CI]	One Week Post Mean (SD) [95% CI]
Executive Function			
CNS-VS	71.57 (31.80) [42.16, 100.98]	91.29 (34.35) [59.52, 123.05]	98.57 (35.41) [65.83, 131.32]
WCST	73.71 (12.51) [62.14, 85.29]	71.42 (10.72) [61.51, 81.34]	74.29 (15.70) [61.76, 90.81]
Verbal Memory			
CNS-VS	85.29 (25.36) [61.84, 108.74]	80.43 (35.90) [47.23, 113.63]	85.86 (26.82) [61.05, 110.66]
CVLT-II	8.57 (3.36) [5.46, 11.67]	10.57 (4.16) [6.73, 14.42]	12.71 (3.99) [9.03, 16.40]
Visual Memory			
CNS-VS	92.57(15.37) [78.36, 106.79]	93.29 (18.69) [76.00, 110.57]	91.00 (25.64) [67.29, 114.71]
RCFT	18.79 (6.40) [12.87, 24.71]	24.29 (9.03) [15.94, 32.63]	27.93 (8.61) [19.96, 35.90]

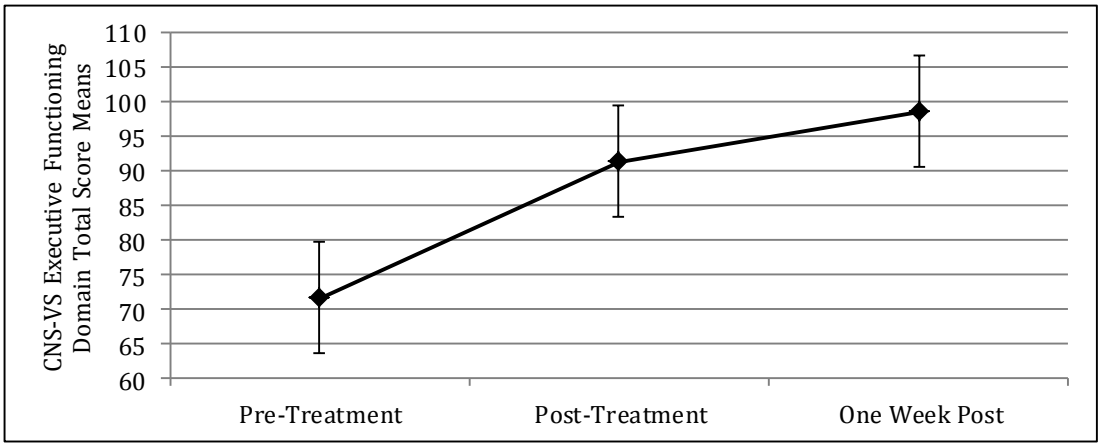

Figure 6. CNS-VS Executive Functioning Domain 3-Time Point Total Score Means

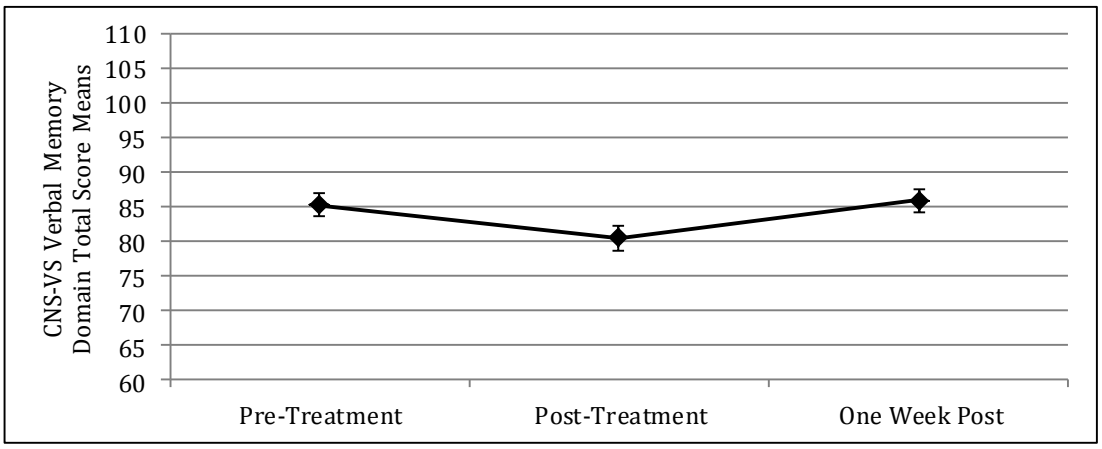

Figure 7. CNS-VS Verbal Memory Domain 3-Time Point Total Score Means

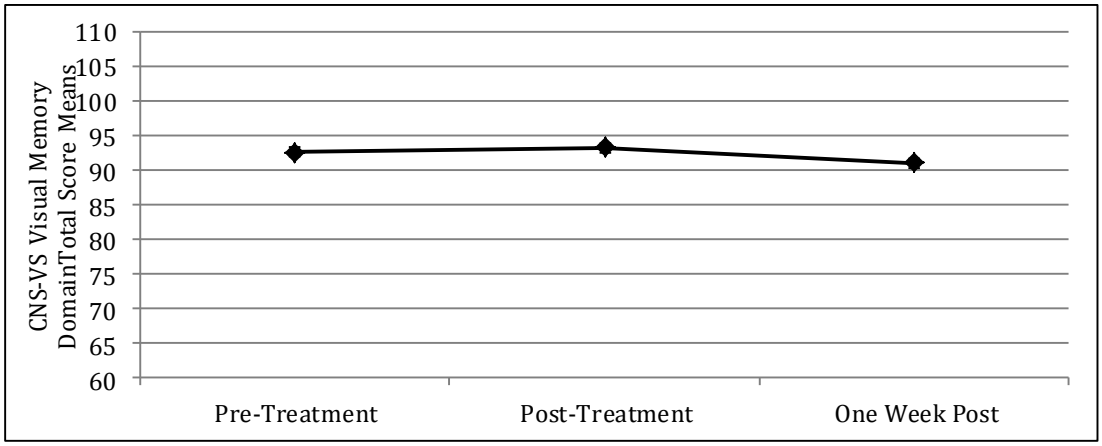

Figure 8. CNS-VS Visual Memory Domain 3-Time Point Total Score Means

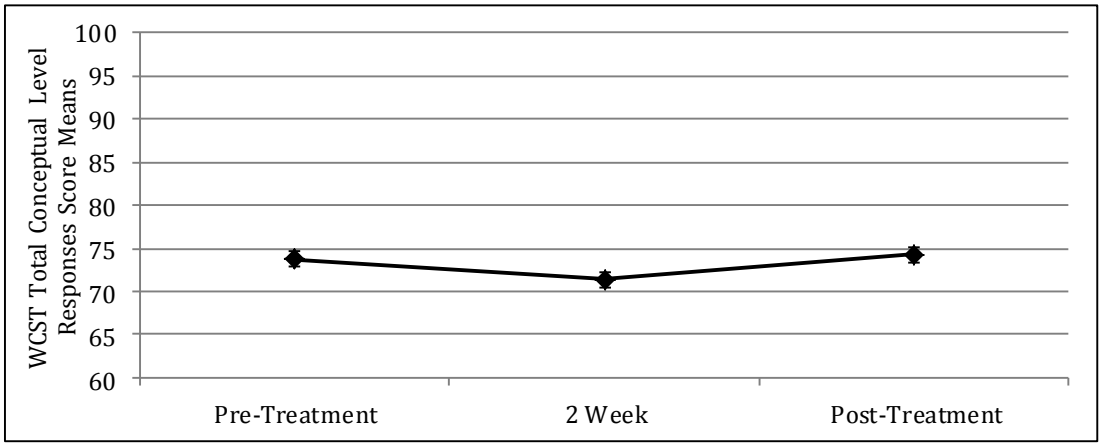

Figure 9. WCST 3-Time Point Total Conceptual Level Responses Score Means

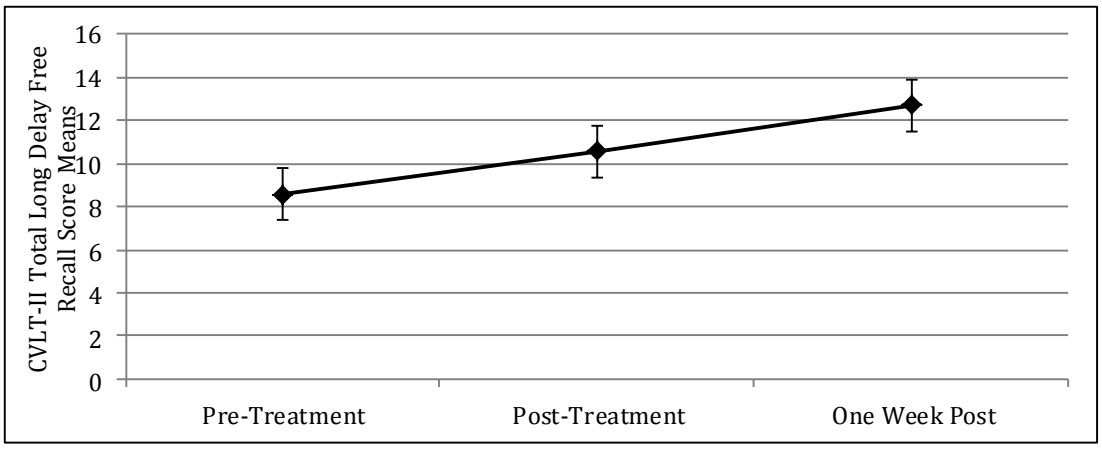

Figure 10. CVLT-II 3-Time Point Total Long Delay Free Recall Score Means

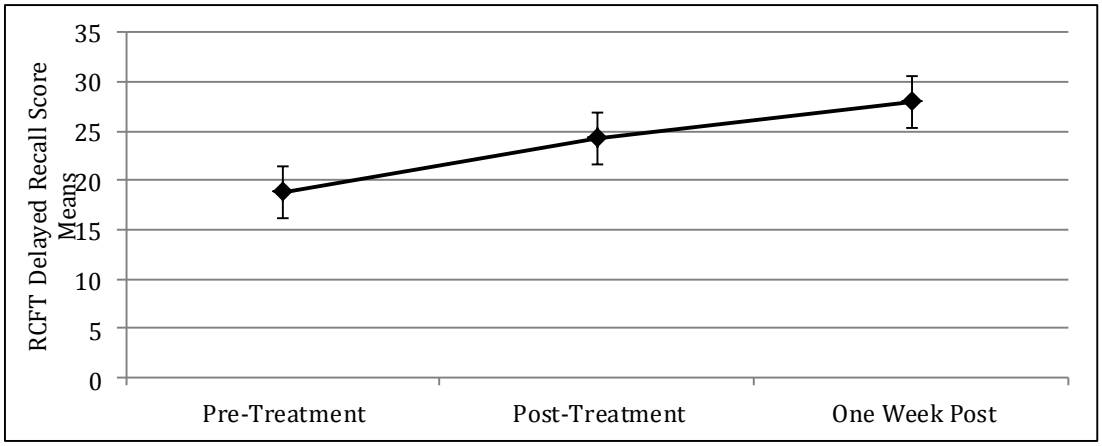

Figure 11. RCFT 3-Time Point Delayed Recall Score Means

CHAPTER IV

DISCUSSION

More than half of PTSD cases are refractory to the current standard of care (Foa et al., 2009; Schnyder, 2005). Thus, PTSD remains a chronic illness for many individuals, despite treatment. In addition to the psychological dysfunction experienced with PTSD, many patients undergo a debilitating decline in neurocognitive functioning (Uddo et al., 1993; Polak et al., 2012). Exposure therapy is currently the most efficacious treatment we have for the treatment of PTSD (Foa et al., 1999; Foa et al., 2005; Foa et al., 1991; Keane et al., 1989; Resick et al., 2002), with limited research suggesting that the addition of TMS to exposure therapy may provide increased benefit over exposure therapy alone (Ousch et al., 2009).

The aim of the present study was to determine if combined TMS and prolonged imaginal exposure was associated with improvements in PTSD symptoms, concomitant depression and anxiety symptoms, and neurocognitive functioning. The goal of this aim was to provide information regarding the safety and utility of TMS combined with imaginal exposure as an additional modality of treatment for PTSD and declines in cognitive functioning that often accompany PTSD. A further aim of the study was to determine if gains associated with the aforementioned treatment were maintained once treatment had been discontinued. More specifically, patients were assessed using self-report and clinician administered questionnaires for PTSD, depression, and anxiety symptoms (PCL-M, TOP-8, BDI-II, HAM-D, and BAI) and neurocognitive tests measuring executive functioning, verbal memory and visual memory (CNS Vital Signs,

WCST, CVLT-II, and RCFT) at pre-treatment, post-treatment, and one week post-treatment.

Major Findings

As mentioned above, limited research suggests that the addition of TMS to exposure therapy may provide increased benefit for reduction of PTSD symptoms (Ousch et al., 2009). However, in this previous study the imaginal exposure procedure differed from the standard exposure therapy protocol in that participants could choose to speak about any past traumatic memory (as opposed to the most distressing memory) or they could choose to be silent during TMS. Further, in this previous study the SMA, which has direct afferent connections to the amygdala and thus a likely role in PTSD symptom maintenance, was not stimulated. Finally, it was unclear in the previous study how many participants were below the clinical threshold for PTSD post-treatment. Consequently, findings needed to be replicated with a more standard exposure therapy protocol, with inclusion of SMA stimulation, and with the inclusion of statistics for percentage of participants who no longer met criteria for PTSD post-treatment.

The procedure used in the present study was well tolerated by this patient sample, with the only reported side effect being brief scalp irritation for two patients with very short hair. No patients dropped out during treatment. This is noteworthy as dropout for standard PTSD treatments is approximately 20% (Foa et al., 2009; Schnyder, 2005). It is highly possible that the added TMS began inhibiting fear-maintaining circuits immediately upon application, thus reducing symptoms quickly enough to prevent dropout due to avoidance. Avoidance is common in PTSD and likely worsens if symptom reduction is delayed during treatment, increasing probability of dropout.

Further research is warranted to examine factors contributing to treatment tolerance with PTSD.

As predicted, results for both measures of PTSD symptom severity (PCL-M and TOP-8) revealed statistically significant reductions in PTSD symptoms from pre-treatment to post-treatment, with reductions remaining stable at one week post-treatment. Effect sizes for both measures were very large, however as sample size is small the likelihood of sampling error is high. One hundred percent of the sample demonstrated clinically significant reductions (more than 10-point change) in PTSD symptoms from pre-treatment to post-treatment on the PCL-M, with 86% (n = 6) of the sample falling below the 50-point cutoff score for a likely PTSD diagnosis by one week post-treatment. Thus, it appears as if 86% of patients no longer had PTSD following treatment. With previous studies using exposure therapy alone indicating that less than 50% of patients recover from PTSD (Foa et al., 2009; Schnyder, 2005), it is possible that the addition of TMS to exposure therapy does provide increased benefit for reduction of PTSD symptoms over exposure alone. Again, comparison across studies is speculative and inconclusive, particularly as there is no standard of care or control group in the present study. Additionally, in the present study there was a 51.4% improvement in PTSD symptoms as measured by the PCL-M, whereas previous studies using only TMS to treat PTSD found 29.3%-36.9% symptom change with the PCL-M. Moreover, all participants in the current study had treatment refractory PTSD, demonstrating that the combination of TMS and exposure therapy may be effective for patients who have not responded to other PTSD treatments. Were this protocol used as a first line treatment, rather than on a

treatment refractory sample, the percentage of those who recover from PTSD could be even greater.

A similar pattern emerged for patients' concomitant depressive symptoms. As expected, results for both measures of depressive symptom severity (BDI-II and HAM-D) revealed statistically significant reductions in depressive symptoms from pre-treatment to post-treatment, with reductions remaining stable at one week post-treatment. Once again, effect sizes for both measures were very large, but sampling error in such a small sample is likely a factor. In terms of clinical significance, 100% of the sample demonstrated clinically significant reductions (as measured by 1 SD in change from the pre-treatment measure) in depressive symptoms from pre-treatment to post-treatment on the BDI-II. At pre-treatment 57% (n = 4) of patients had severe depression as per the BDI-II and the remaining 43% (n = 3) had moderate depression. By one week post-treatment, 14% (n = 1) of the sample had moderate depression, with 86% (n = 6) of the sample falling below the 14-point cutoff score for mild depression. Thus, it is possible that 86% of patients no longer had clinically significant depression following treatment.

Comorbidity studies indicate that depression is one of the most commonly co-occurring disorders with PTSD, with approximately 48% of those with PTSD also having current or past depression. Those who have had PTSD at some point in their lives are almost 7 times as likely as people without PTSD to also have depression (Breslau, 2002; Kessler et al., 2005; Shalev et al., 1998). In the present study comorbid depression was even more prevalent, with 100% of the sample having co-occurring depression as per the BDI-II. It may be that comorbid depression contributes to PTSD being chronic and treatment resistant, thus explaining the difference in comorbidity percentages. PTSD and

depression may be connected in a number of ways, but the mechanism behind the connection is not abundantly clear in the literature. Those with depression have been found to be more likely to have traumatic experiences than people without depression, which in turn, may increase the likelihood that PTSD develops (Shalev et al., 1998). A second possibility is that the symptoms of PTSD can be so distressing and debilitating that they cause depression to develop. While co-morbid disorders can be considered confounds in treatment studies, given the high co-occurrence of PTSD and depression in the general population, it could be argued that the improvements of both disorders with the present treatment renders the combined treatment utilized in the present study more useful and more ecologically valid. Regardless of the mechanism of action connecting these disorders, it can be postulated that a treatment associated with remission of both PTSD and depressive symptoms in 86% of those treated has disrupted the cycle of PTSD leading to depression, depression leading to PTSD, and so forth.

Regarding anxiety symptoms that are not specific to PTSD, as predicted, results measured by the BAI revealed a statistically significant reduction from pre-treatment to post-treatment, with this reduction remaining stable at one week post-treatment. Once again, the effect size was large, but subject to sampling error due to the small sample size. In terms of clinical significance, only 43% (n = 3) of the sample demonstrated significant reductions (as measured by 1 SD in change from the pre-treatment measure) in anxiety symptoms from pre-treatment to post-treatment on the BAI. This can be explained, at least in part, by the fact that pre-treatment scores were not as high for concomitant anxiety symptoms as they were for concomitant depression scores. Forty three percent of patients reported only mild levels of anxiety at baseline, whereas all

patients reported moderate to severe levels of depression. Thus, there was less room for clinical improvement with regard to anxiety. This is expected, given that comorbid anxiety diagnoses are less common than comorbid depression with PTSD (Kessler et al., 2005). Two of the three patients with severe anxiety at baseline had clinically significant improvement, with the third patient being the one who experienced a confounding adverse event during the study.

The second research question examined whether combined TMS and exposure therapy was associated with changes in neurocognitive functioning, including executive functioning, verbal memory and visual memory. Declines in these cognitive domains have been associated with PTSD (Polak et al., 2012; Uddo et al., 1993). Computerized neurocognitive tests (CNS-VS) as well as more traditional, well established neuropsychological tests (WCST, CVLT-II, and RCFT) were used to assess neurocognitive functioning with mixed results. Specifically, results from the CNS-VS measures did not appear to coincide with results from the more traditional measures.

In the domain of executive functioning, analyses of the CNS-VS Executive Functioning Domain demonstrated statistically significant improvement in executive functioning with a large effect size, but again this must be interpreted with caution due to the likelihood of sampling error. However, the traditional neuropsychological measure (WCST) revealed no significant differences from pre-treatment to post-treatment. The most likely explanation for the difference is that the tests were not measuring the same construct. Upon closer examination, the CNS-VS Executive Functioning score is comprised of the results from two computerized tests, the Stroop Test (measuring selective attention, ability to inhibit, and executive processing speed) and the Shifting

Attention Test (measuring decision making, set shifting, and reaction time). The WCST measures primarily pattern recognition and set shifting. And so, the CNS-VS test is a much broader measure of executive functions, whereas the WCST is more specific. As such, results may indicate that the present treatment improves executive functioning broadly, but does not specifically improve set shifting and pattern recognition. A second explanation could be that patients' reaction time and processing speed improved, which in turn improved CNS-VS scores, but not WCST scores as time was not a factor on that test. A third possible explanation is that the small sample size resulted in a type II error for the WCST findings. However, this is unlikely as the means and SDs for the WCST remained approximately equal across all three time points.

With regard to verbal and visual memory, the reverse pattern was found. Namely, there were no significant improvements on CNS-VS Domain scores (Verbal Memory and Visual Memory Domains), but there were statistically significant improvements on the more traditional neuropsychological measures (CVLT-II and RCFT), with large effect sizes. Again, the most likely explanation is that the CNS-VS tests and the traditional measures were not measuring the same constructs.

One major difference between the CNS-VS Verbal Memory Domain test and the CVLT-II is that the stimuli are presented in differing modalities. Specifically, they are presented visually (on a computer screen) for CNS-VS and verbally (spoken by the test administrator) for the CVLT-II. Thus, the CNS-VS test requires visual attention and encoding circuitry, whereas the CVLT-II requires auditory attention and encoding circuitry. Furthermore, the CNS-VS Verbal Memory Domain test is an assessment of recognition memory (recognizing the correct words, which are nested among distractors),

but the measure examined on the CVLT-II is a test of free recall. A third difference is that words are repeated five times during the encoding phase of the CVLT-II to optimize learning. However, the CNS-VS presents words only once. So, it may be concluded that the present treatment is associated with improvements in auditory attention and encoding of verbal information and delayed free recall of said information, when information is repeated several times during the encoding phase. However, the treatment was not associated with improvements in visual attention and recognition memory of verbal information that is presented only once during the encoding phase. A practical assessment of these findings may be that patients will likely have improved memory for conversational information, but not for information they have read.

A final distinction between the CVLT-II and the CNS-VS Verbal Memory test is that the CVLT-II presents words belonging to four categories (animals, forms of transportation, vegetables, and furniture) whereas the CNS-VS test presents words that are not associated with one another in any apparent way. This distinction is important, because the ability to categorize and associate words as a strategy for remembering requires intact executive functions. The finding discussed above that the present treatment is associated with broad improvements in executive functioning may help explain why improvements were seen on the CVLT-II, with its high degree of executive involvement, but not on the CNS-VS Verbal Memory test, which does not involve the same degree of executive functioning. Therefore, another explanation for the differing results between the CVLT-II and the CNS-VS Verbal Memory test is that the mechanism of action behind the improvement in verbal memory is actually through the enhancement in executive functioning, rather than a direct improvement in verbal memory. This

explanation is supported by previous research indicating that executive functioning, as measured by Wisconsin Card-Sorting Test, Trail-Making Test-Part B, Controlled Oral Word Association Test, Animal Naming, and Wechsler Adult Intelligence Scale-Third Edition Similarities, accounted for substantial variance (24%-31%) in CVLT-II performance for the Long-Delay Recall index (Hill, Alosco, Bauer & Tremont, 2012). The literature also indicates correlations between the CVLT-II Long-Delay Recall index and select subtests of the D-KEFS, a standardized battery of executive functioning (Delis, Kaplan & Kramer, 2001a; Delis, Kaplan & Kramer, 2001b).

The tests of visual memory are more similar than those for verbal memory, but there are some important differences. Most notable again is the organizational component of the RCFT. The RCFT requires the test taker to not only remember visually presented shapes, but he also must remember how those shapes were organized on the page. Thus, the test taker must utilize the executive functions of planning and organization in addition to visual memory. The CNS-VS Visual Memory Domain test does not have this organizational component. And so again, the mechanism of action behind the improvement in visual memory may actually be through an enhancement in executive functioning, rather than a direct improvement in visual memory. Qualitative findings support the role of executive functioning in RCFT performance (Stern et al., 1995; Watanabe et al., 2005) but this relationship is not well established as yet through quantitative research.

A second difference between the tests is that the CNS-VS Visual Memory Domain test is an assessment of recognition memory (recognizing the correct shapes, which are nested among distractors), but the measure examined on the RCFT is a test of

free recall. It may be that the present treatment improves visual free recall but not recognition memory, or again it may be that the mechanism of action behind the improvement is through the enhancement in executive functioning, rather than a direct improvement in visual memory; irrespective of which interpretation is accurate, what is certain is that the use of a variety of assessments to test what may assumed to be a single construct is important for an in-depth understanding of possible treatment effects. While results on measures of psychological symptoms coincided well, results for tests of neurocognitive functioning were more complex. The use of multiple assessments for each domain allowed for a more considered and detailed appreciation of cognitive changes.

A final explanation for the inconsistent findings with regard to neurocognitive functioning pertains to the shortcomings of statistical analyses with a small sample. Namely, the nonsignificant results may be attributable to underpowering. Conversely, the significant results may be due to practice effects or other confounds. These potential limitations are discussed further below.

Limitations and Design Considerations

A major limitation of the current study is the small sample size. Although a power analysis determined that a sample size of seven was sufficient for a large effect size, if the effect sizes were smaller, a larger sample would be required to detect those effects. Thus, potentially significant results with small or even medium effect sizes may have been missed due to underpowering. For instance, it may be that with a larger sample, improvement in other cognitive domains more distal from treatment areas would be detected. The small sample size is also problematic in that it may not be a good

representation of the general population due to likely sampling error in a sample of seven. Patient recruitment was the primary limiting factor in terms of sample size. This may have been due to several causes, including the continued lack of awareness and misunderstandings about TMS. The general population, as well as many healthcare providers, likely equate any external brain stimulation to ECT, and consequently assume it has a high likelihood of undesirable side effects. This may have contributed to a reluctance to refer patients to the study. It was also the case that two potential participants expressed initial interest, but did not attend any sessions after hearing a summary of what the treatment entailed. It is impossible to say what prevented them from attending, but uncertainty about brain stimulation may have been a factor. Recruitment was also likely limited by the tendency for those with PTSD to avoid situations that require them to think about their traumatic events.

Generalizability of the findings is further limited as the sample consisted only of men with combat trauma. While this homogeneity is preferred with such a small sample, attempts to generalize these findings to women with PTSD or those with non-combat related PTSD should not be done yet. The literature does show that prolonged exposure is effective across gender and type of trauma (military and non-military; Foa, et al., 2009). As such, generalizability of the effects of the current treatment protocol to women and non-combat trauma seems promising, but replication and more diverse sampling is needed in the future.

Selection bias is an additional limiting factor as patients self-selected to be a part of the treatment. As a result, the sample includes only patients who were willing to undergo a novel and lengthy treatment and set of assessments. They must, as noted

above, also have been willing to repeatedly recount their past trauma in detail. This willingness may be an unlikely characteristic of patients with PTSD. A randomized controlled trial would control to some degree for selection bias as well as the potential confounds of maturation, order effects such as practice, boredom and fatigue, and the influence of events outside the experiment, but it would not account completely for the selection effect of patients willing to participate in a lengthy study.

A double-blind, randomized controlled trial would also help to control for observer-experimenter expectancy bias, which may have contributed to significant results. As there was no control group, participants were aware that they were receiving an innovative and novel treatment, thus they may have expected to improve. This expectation could have influenced them to report decreased symptoms more readily. Additionally, there may have been expectancy bias on the part of the treatment administrators due to the lack of a double-blinded study design. Because this pilot study suggested clinical improvements and demonstrated the viability of the treatment, further research incorporating blinded, randomized assignment to either a treatment group or a control group is warranted. Ideally, further research would also require those administering treatment to be blinded to the condition by utilizing sham TMS for the control group. These study design improvements would eliminate observer-experimenter expectancy biases. In view of the limitations discussed in this paragraph, it may be that part of the effects found are attributable to a placebo effects rather than the treatment itself.

Future research should also include more long-term follow-up if possible. While a post-treatment measure was utilized in the present study, it was taken only one week

post-treatment taper (4 weeks post daily treatment). Durability of this treatment needs to be assessed at 3 months, 6 months, etc, particularly as preliminary research on TMS to treat major depressive disorder indicates a substantial percentage of those who respond to treatment require maintenance sessions to prevent relapse (Fitzgerald, Grace, Hoy, Bailey & Daskalakis, 2013; Richieri et al., 2013). Mounting data on the durability of TMS treatment for refractory depression do suggest that the therapeutic effects of TMS are durable and that TMS may be successfully used as an intermittent rescue strategy to preclude impending relapse (Janicak, et al., 2010). If the need for maintenance treatment is determined, further research on various maintenance protocols should be conducted to determine frequency and duration of sessions.

The potential for improvement of cognitive functioning due to a psychological intervention is another limiting factor in interpreting the results of the present study. Previous research has found that neurocognitive changes do take place independent of psychological changes following TMS (Bayan, 2014; Vanderhasselt, Raedt, Baeken, Leyman & D'Haenen , 2009). These previous findings are corroborated by results in the present study indicating improvement in executive functioning, which is most associated with a brain region receiving direct TMS stimulation (DLPFC), but no improvement in non-executive memory, which is most associated with a brain region not directly stimulated (temporal region). In other words, cognitive gains were only shown for areas where TMS was applied directly. Additionally, regression analyses were conducted to examine the relationship between neurocognitive test score changes for measures that showed statistically significant improvement from pre- to post-treatment (CNS-VS Executive Functioning Domain, CVLT-II, and RCFT change scores) and change scores

from pre- to post-treatment for measures of psychological symptom change (PCL-M, TOP-8, BDI-II, HAM-D and BAI change scores). Results revealed that change scores for psychological symptoms did not significantly predict neurocognitive change scores in any of the regression analyses ($p < .05$). *B* values for all regression analyses can be seen in Table 5. These results are noteworthy due to their implications for the potential treatment of neurocognitive deficits associated with other neuropsychiatric and neurological illnesses or injuries. This finding replicates previous research demonstrating the functional impact of TMS' role in stimulating neuronal activity in focal regions of the brain implicated with particular cognitive functions (Bayan, 2014). Even so, further research is warranted to better explain the mechanism of action behind the cognitive improvements. It is worth stating however, that cognitive improvements are almost definitely beneficial to the patients regardless of mechanism of action.

Table 5

B Values Indicating the Relationship between Neurocognitive Test Score Change (CNS-VS Executive Functioning Domain, CVLT-II, and RCFT) and Psychological Symptom Change (PCL-M, TOP-8, BDI-II, HAM-D and BAI)

	PCL-M	TOP-8	BDI-II	HAM-D	BAI
CNS-VS-EF	.41	-1.35	-3.54	2.56	-.04
CVLT-II	.57	-.34	-.74	.52	-.11
RCFT	.54	-.66	-.75	.79	-.18

* = $p < .05$; ** = $p < .01$; ***= $p < .00$

A final consideration for future research designs concerns what to include in the battery. As many measures were utilized in this study, psychological symptoms were assessed using brief screening measures (PCL-M, TOP-8, BDI-II, HAM-D, BAI) for the sake of efficiency. However, the gold standard for PTSD assessment is the CAPS. Future studies focusing solely on PTSD may want to incorporate the CAPS to measure symptom reductions and not just as an initial interview to determine PTSD diagnosis.

In terms of the neurocognitive battery, interpretation of the results is limited by the fact that, as noted in the Methods section, the psychometrics of the tests used were not determined with a sample of men who have PTSD. Rather they are primarily from samples of normal controls. Thus, generalizing the psychometric properties to the sample in the present study must be done cautiously. There is no body of literature looking at the psychometrics of neurocognitive tests in populations with PTSD. When examining the properties of neurocognitive tests in clinical samples, the focus is often on patients with overt brain injuries or neurodegenerative processes, and these are not appropriate comparison groups for the present sample. Further research examining the psychometrics of commonly used neurocognitive tests in those with PTSD is a much needed addition to the literature.

Furthermore, the neurocognitive battery chosen for this study could be considered problematic as it did not prove consistent across cognitive domains. In other words, the two executive functioning measures did not show equivalent outcomes. The same inconsistency was found for the measures of verbal and visual memory. However, use of multiple neurocognitive measures for a single cognitive domain does provide a more comprehensive view of neurocognitive changes, as well as the limitations in cognitive

change. Although results may appear contradictory on the surface, a thorough interpretation of scores and in-depth understanding of what each assessment measures reveal a more accurate, albeit complex, representation of cognition.

Conclusions

The present study was able to contribute to the current literature regarding TMS as a safe and beneficial treatment for psychological and neurocognitive symptoms. Specifically, this study provides support for the use of TMS as a treatment for chronic, treatment refractory PTSD in men with combat trauma. Results further indicate that the benefit of low frequency TMS to the RDLPFC and the SMA combined with prolonged imaginal exposure may exceed the effect of exposure therapy alone and the effect of TMS alone, as measured by symptom improvement percentages from previous studies.. However, this comparison is merely speculative and requires further research to confirm. This treatment protocol was also associated with reductions in concomitant symptoms of depression and anxiety, which are often debilitating comorbidities in those with PTSD. The clinical improvements associated with the present protocol propound a strong case for a larger double-blinded RCT examining the statistical significance of the present treatment protocol as compared to a control. If the results of this pilot study are replicated in a RCT, the case will be strong for offering this as an FDA approved treatment for chronic, treatment resistant PTSD. Further, the low side-effect profile indicates the protocol used in the present study may be appropriate as a first line treatment for PTSD, if patients do not have any contraindications to TMS.

With regard to neurocognitive function, the present treatment protocol was associated with improvements in general executive functioning, but not set-shifting

specifically. Executive functions, often thought of as central command for the brain, play an integral role in decision making and behavioral guidance. Improvement in these abilities for those with PTSD, many of whom have a post-diagnosis history of poor decisions and disordered behavior, will likely lead to improved functioning and better overall quality of life. Results for tests of verbal and visual memory were inconsistent, but generally indicate that executive memory is improved both in both verbal and visual domains. However, results on memory tests that do not have an executive component did not show improvement. This finding may indicate that cognitive changes are more likely in domains associated with the areas of the brain receiving direct stimulation, in this case the prefrontal cortex (associated with executive functions), but not as likely for domains associated with areas of the brain that must be reached transsynaptically. Many components of the memory process are associated with the temporal lobes, which were not directly stimulated in this protocol, and thus may be less likely to show improvements. It may also be that cognitive changes associated with areas of the brain treated transynapically occur, but only after a longer period of treatment. This latter explanation bears some weight given that neuroimaging studies have demonstrated metabolic and cerebral blood flow alterations in limbic and paralimbic areas of the brain that cannot be directly stimulated, and thus must be reached transynaptically (Kito, Fugita & Koga, 2008; Kito, Hasegawa & Koga , 2012; Speer et al., 2000). Neurocognitive changes were not predicted by measures of psychological change in several regression analyses, indicating neurocognitive changes likely occur independent of psychological changes. This is noteworthy due to its implications for the potential treatment of neurocognitive deficits associated with other neuropsychiatric and neurological illnesses

or injuries. The results of the present study help to further elucidate how functional processes may be altered by the changes seen on neuroimaging in previous studies. However, it must be restated that all conclusions are tentative due to the likelihood of sampling error and potential confounds.

In summary, this is the first pilot study of its kind to combine TMS to the right DLPFC and the SMA with a standardized exposure protocol for the treatment of chronic, treatment-resistant PTSD. The aims were to (1) determine if the treatment was safe and well tolerated, (2) determine if PTSD and concomitant depression and anxiety symptoms improved, and (3) determine if executive functioning and memory improved. The treatment was safe and well tolerated, and improvements were seen across measures with the exception of non-executive memory, although statistical significance must be viewed tentatively. Most strikingly, six of the seven participants no longer met criteria for PTSD by the end of the study. A PTSD treatment that improves psychological and neurocognitive symptoms with minimal side effects has immense utility in improving functionality and quality of life for combat veterans, and possibly for other populations with PTSD. Results for this pilot study are promising, but larger studies utilizing a RCT model are needed to confirm and expand upon these very preliminary findings. If findings are well confirmed, steps for FDA approval of the procedure used in the present study would be warranted.

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APPENDIX

Table 6

Correlations between Potential Covariates and CNS-VS Neurocognitive Domain Scores (Executive Functioning, Verbal Memory, Visual Memory) at 3 Time Points (Pre-Treatment, Post-Treatment, 1 Week Post-Treatment)

Variables	Executive Function			Verbal Memory			Visual Memory		
	Pre	Post	1WP	Pre	Post	1WP	Pre	Post	1WP
Baseline PCL-M	-.14	.39	.29	.33	.59	.20	.20	.05	.33
Baseline TOP-8	.00	.26	.16	.21	.32	.00	-.16	.00	.41
Baseline BDI-II	-.29	.25	.15	.20	.55	.25	.25	.10	.20
Baseline HAM-D	-.20	.15	.05	.39	.35	.15	-.05	.29	.49
Baseline BAI	-.33	.20	.10	.14	.39	.20	.20	.05	.14
Age	-.59	-.15	-.05	-.39	-.25	.05	.15	-.29	-.49
Education Level	.44	.33	.37	.20	.16	.44	.42	.30	.07
Race	.46	.32	.30	.17	.18	-.04	.10	-.07	.05

* = $p < .05$; ** = $p < .01$; ***= $p < .00$

Table 7

Correlations between Potential Covariates and WCST, CVLT-II, and RCFT scores at 3 Time Points (Pre-Treatment, Post-Treatment, 1 Week Post-Treatment)

Variables	WCST			CVLT-II			RCFT		
	Pre	Post	1WP	Pre	Post	1WP	Pre	Post	1WP
Baseline PCL-M	-.29	-.15	-.43	.49	.62	.59	-.33	.10	.24
Baseline TOP-8	-.37	-.32	-.41	.16	.51	.32	.10	.26	.10
Baseline BDI-II	-.45	-.10	-.39	.35	.49	.55	-.39	-.05	.10
Baseline HAM-D	-.20	-.26	-.29	.15	.20	-.15	.00	.05	.25
Baseline BAI	-.29	-.05	-.24	.49	.43	.59	-.52	-.10	.05
Age	-.20	.46	.49	-.15	-.20	-.05	-.39	-.65*	-.49
Education Level	.81*	.26	.20	-.07	-.12	.20	.42	.36	.45
Race	-.13	-.10	-.28	.60	.41	.15	-.27	.09	.10

* = $p < .05$; ** = $p < .01$; ***= $p < .00$

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Select Publications and Presentations

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