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Cognitive Performance as A Function of Right-Sided, Low-Frequency rTMS Administration Using CNS Vital Signs

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by

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ABSTRACT

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Major Depressive Disorder (MDD) is a complex, widespread, and recurrent psychiatric disorder. Although the majority of affected individuals respond adequately to pharmacotherapy and/or psychotherapy, there persists a sub-population of affected individuals who do not improve despite these interventions. Electric convulsive therapy has been described in the research as the most efficacious options for treatment resistant depression. However, due to the neurocognitive deficits associated with ECT, interest in transcranial magnetic stimulation (TMS), a non-invasive approach that stimulates the cerebral cortex, as an alternative to ECT has become a major research focus. The efficacy of both high-frequency and low-frequency rTMS for depression have been well documented although the impact on neurocognitive functioning is not completely understood. Research to date has demonstrated neurocognitive improvement following rTMS to the left dorsolateral prefrontal cortex only. Therefore, this study focused on the neurocognitive changes associated with rTMS when administered to the right dorsolateral prefrontal cortex and the supplementary motor area, utilizing data from the existing EVMS registry for patients receiving TMS. Measures assessed depression (Beck Depression Inventory-II), anxiety (Beck Anxiety Inventory), and neurocognitive functioning (CNS-Vital Signs tests of executive function, cognitive flexibility, and

complex attention). A series of ANOVAs were conducted to examine: a) whether statistically significant differences exist in neurocognitive scores following 2 and/or 6 weeks of rTMS treatment as compared to pre-treatment; and b) whether any significant improvements in neurocognitive scores occur independent of a reduction in depression and anxiety scores. As expected, results revealed statistically significant improvements for all three neurocognitive domains across all three time points with the greatest improvement taking place during the first two weeks of treatment with a stabilizing effect thereafter. Results also revealed changes in depression and anxiety scores that were not significantly correlated with Executive Functioning, Complex Attention, and Cognitive Flexibility change scores. Therefore this study substantiates the use of right-sided, low-frequency rTMS as a treatment alternative to ECT as it provides support for improved cognitive functions that occur independent of mood improvements.

This dissertation highlights one of the more significant milestones associated with an academic journey that at times, I never thought possible. It is dedicated to my family and to my best friends. Your belief in me provided solace in the most difficult moments and the under the most intimidating circumstances. I love and appreciate all of you more than you will ever know.

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CHAPTER 1

INTRODUCTION

The primary aim of the present study is to examine possible neurocognitive improvements associated with the recommended clinical dose of repetitive Transcranial Magnetic Stimulation (rTMS) in the treatment of resistant depression when administered to the right dorsolateral prefrontal cortex and supplementary motor cortex. While existing research supports enhanced cognitive functions following left-sided applications of rTMS, right-sided applications remain unexplored. As the efficacy of rTMS for treatment resistant depression continues to be established through recent and ongoing research, the importance of elucidating its impact on the neurocognitive features associated with Major Depressive Disorder (MDD) is paramount. This is particularly true considering the established neurocognitive deficits resulting from the predecessor to rTMS, electroconvulsive therapy (ECT). Therefore, the superiority of rTMS in the treatment of refractory depression, not only demands equitable or increased efficacy as compared to ECT, but also enhanced neuronal and neuropsychological changes resulting from its application.

The remainder of this introduction includes a more thorough discussion of the rationale for the study along with an overview of both low and high frequency Transcranial Magnetic Stimulation (TMS). The epidemiology and treatment options for depression and more specifically, treatment-resistant depression are also addressed. In addition, an overview of the current structural and functional abnormalities and neurocognitive deficits associated with depression and the impact of TMS on these abnormalities will be included. These sections demonstrate the trend toward the use of

TMS in the treatment of depression and provide justification for a study of this nature. The final section will integrate the preceding sections and provide the final validation for this study and the study hypotheses.

Rationale of the Current Study

Major Depressive Disorder (MDD) is not only widespread, but it also tends to be recurrent. In fact, it is among the most prevalent of all psychiatric disorders. Up to 20% of the general population will experience at least one episode of depression throughout their lifetime and 80% of those affected will experience a relapse of symptoms. Despite the advancements made possible through neuroimaging as well as through genetic and molecular studies, depression remains a complex disorder characterized by vast heterogeneity (Gotlib & Hamilton, 2008). What is more, there persists a considerable sub-population of affected individuals who do not improve despite the use of psychopharmacological and psychotherapeutic interventions. It is treatment-resistant depression (TRD), with its debilitating nature and high economic cost, that has prompted a shift from targeting synaptic transmission for treatment, which fails to completely account for depressive symptomology, to a more comprehensive focus on neural circuitry (O'Reardon, Peshek, Romero, & Cristancho, 2006).

Treatment-resistant depression, a term reserved for a lack of remission despite antidepressant treatment in adequate doses (or intensity) and for a time sufficient for response, has in large part, driven the research for Transcranial Magnetic Stimulation (TMS) (Fava & Davidson, 1996). To date, electric convulsive therapy (ECT) has been considered the most efficacious treatment for TRD. ECT is not without its drawbacks however. Unlike rTMS, which is applied painlessly to awake patients, ECT utilizes

direct transcranial electrical currents, which requires patients to be anesthetized to ensure comfort and to facilitate the administration of muscle relaxation. Aside from its invasive nature and need for sedation, ECT has also been criticized for resulting in cognitive side effects. Specifically, ECT has been shown to produce anterograde amnesia, retrograde amnesia and subjective memory complaints (Schulze-Rauschenbach, Harms, Schlaepfer, Maier, Falkai, & Wagner, 2005). For these reasons, interest in TMS, a non-invasive approach that stimulates the cerebral cortex, as an alternative to ECT has become a major research focus.

Transcranial magnetic stimulation is not the first use of magnets for healing. It is however unique in its application. With the use of a pulsed electromagnetic field to modulate neuronal activity in the cortex, TMS has been shown to produce antidepressant actions. Some studies have even reported that the efficacy of TMS extends to the maintenance treatment of depression (Wang, Xue, Chen, Zhang, Wnag, Yahong, Jingli, Zhang, & Qingrong, 2013). The magnitude and breadth of potential of applicability for rTMS for psychiatric and medical patients however is yet unknown. At present, the FDA has approved rTMS for only a marginal sector of the patients. For its benefits to be more fully known and for it to be approved more broadly by the FDA, all risks and benefits must be scientifically demonstrated. Among these are any cognitive benefits and/or impairments resulting from rTMS. This makes research into this inquiry and the dissemination of findings to clinicians and patients alike, critical.

Like many psychiatric and medical conditions, depression is associated with neurocognitive dysfunction. This has been confirmed not only through subjective reports and neuropsychological testing, but with the advances of neuroimaging techniques as

well. In fact, through these latter techniques, functional and structural abnormalities help differentiate individuals with MDD from normals. They also confirm the need for depression subtypes (e.g. symptom-based, aetiologically-based, time of onset, gender based, and treatment-resistent) and have helped pave the path for specific and individualized treatment options.

Overview of Transcranial Magnetic Stimulation (TMS)

The knowledge that nerves and muscles can be externally stimulated via applied electrical currents has long since been established. In fact, initial experiments date back to the 1790s and the work of Galvani and Volta. The term magnetic stimulation is a bit misleading, however, as the magnetic field created during its administration does not itself directly stimulate the tissue. Rather, the magnetic field pulse induces an electrical field in the tissue, which causes an ionic current to flow. If in turn, the amplitude, spatial characteristics, and duration of this induction cause depolarization of a nerve membrane, then stimulation will occur (Barker & Freeston, 2007). The earliest application of rTMS was used to explore susceptibility to seizure induction following stimulations of the motor speed area of the dominant frontal lobe, the area thought to be the most epileptogenic area of the brain. It was through these studies that the added ability of rTMS over single-pulse TMS to produce sustained and spatially selective interruptions of organized neural activity was discovered. Repetitive Transcranial Magnetic Stimulation (rTMS) has lead also to the non-invasive mapping of cognitive and perceptual processes in the human cortex (Wassermann, 1998).

The early 20th century marked the development of magnetic stimulation as a clinical technique. The past 15 years however that have been pivotal in the discovery of

the effectiveness of rTMS as a treatment for depressive disorders in particular. In 2008, the United States approved rTMS for clinical use. Since that time, the interest in the therapeutic effects of rTMS on depression among psychiatrists, neurologists, basic scientists, and the public at large has surged (Fitzgerald & Daskalakis, 2012).

Treatment for depression, using rTMS involves a rapidly timed variable magnetic field applied to a localized area of the cortex. The term repetitive refers to paced administration of TMS to a single scalp site. Although only a restricted area receives direct stimulation (with conventional equipment, TMS penetrates no further than 1.5-2cm beneath the scalp), distal brain activity is impacted as well (Barker, 1991). It is through the TMS coil that an electrical current is allowed to travel, without resistance, into the brain. When the current passes through the coil, a magnetic field is produced and it is this field, when provided above a certain threshold, that ignites electrical activity in the underlying cortical neurons. Over time, with repeated firing, neurons will progressively change their activity. High-frequency stimulation, the most researched TMS application, for example, is known to produce an increase in local cortical excitability (Bohning, Shastri, McConnell, Nahas, Lorberbaum, Roberts, Teneback, Vincent, & George, 1999).

The intensity of TMS is usually given as a percentage of the threshold intensity for evoking motor evoked potentials (MEPs) of a certain amplitude in a specified fraction of a series of consecutive trials in a hand muscle. Response thresholds to TMS vary considerably. Therefore measures of intensity are formulated on the basis of biological efficacy in the individual rather than the output of the stimulator itself. rTMS dosing is determined on an individual bases with the use of an individual's resting motor threshold (RMT). This is established through the administration of individual TMS pulses to the

motor cortex in order to identify the lowest intensity required to consistently induce a motor response in a peripheral muscle, usually the abductor pollicis brevis, in the contralateral hand. RMTs are lowest in the muscles of the hand due to the abundance of the corticospinal projections that rely on their spinal motor neurons (Hanajima, Wang, Nakatani-Enomoto, Hamada, Terao, Furubayashi, Okabe, Inomata-Terada, Yugeta, Rothwell, & Ugawa, 2007). Antidepressant effects are observed from 90% to 120% of the RMT, allowing for intensity reduction if treatment is not being well tolerated. However, there does appear to be a relationship between intensity and efficacy, thus, reductions should be limited (Loo, McFarquhar, & Mitchell, 2008).

TMS is most often administered at a high-frequency to the left dorsolateral prefrontal cortex (DLPFC) at between 5 and 20 Hz. However, other stimulation sites are now being targeted for research and clinical application. Two such sites are the right prefrontal cortex and the supplementary motor area, using a low-frequency stimulation. Low-frequency refers to stimulus rates of 1 Hz or less. Where high-frequency TMS results in cortical excitability, low-frequency creates the opposite effect (Fitzgerald, Fountain, & Daskalakis, 2006). Although it has not been as extensively researched, TMS applied in low-frequencies to the right dorsolateral prefrontal cortex has also been found to be efficacious when evaluated alone and equally efficacious when compared to the left-sided approach. Currently, one meta-analysis exists on right-sided treatment and one multisite sham controlled trial is being conducted, though no results are yet in print (Schutter, 2009). Advantages of right-sided administration include, less demand on equipment and thus fewer concerns about coil overheating, it tends to be better tolerated and more comfortable, and it has a decreased risk of seizure induction. For these reasons,

it can be used when high-frequency doses may exacerbate the existing anxiety experienced by many depressed patients, when patients have a high RMT or a low threshold of tolerance for high-frequency administration, or when there is evidenced likelihood of seizure activity (Santiago-Rodriguez, Cardenas-Morales, Harmony, Fernandez-Bouzas, Porras, Kattz, & Hernandez, 2008).

Regardless of the lateral site, TMS is typically provided five days a week for a duration of two to nine weeks. There are studies currently exploring various treatment-scheduling options to optimize efficacy and efficiency, but the current recommendations suggest that treatment should be provided five times per week unless the patient can only attend three to four times per week, which may not undermine efficacy (Turnier, Bruno & Pridmore, 2006). Regarding treatment duration, there is no clear maximum number of treatments, but most studies support a minimum of six weeks. Subtle mood improvements are typically expected in the second or third week, but others take longer. If improvements are not noted after four weeks of treatment, a change in stimulation site or intensity can be considered (Fitzgerald, Benitez, de Castella, Brown, Daskalakis, Kulkarni, 2006).

Most studies evaluating the efficacy of TMS have involved patients who are not on antidepressant medication. However, there are several trials that have included patients on concurrent treatment and patients who began a pharmacotherapy trial at the start of TMS treatment. The findings of these studies did not produce results suggestive of benefit over sham. It has been speculated that this may be due to alterations in RMT that interfere with treatment. For partial responders where medication is maintained throughout TMS, it is recommended that RMT be assessed regularly and TMS dose be

adjusted accordingly (Herwig, Fallgatter, Hoppner, et al., 2007).

By its very nature, depression is a relapsing disorder; treatment responders to TMS are no exception. However, the rate of relapse lends support to the efficacy of the long-term benefits of TMS. For example, in their study including 99 patients who received rTMS and were then tracked for 24 weeks, Janicak, Nahas, Lisanby et al., (2010) found that only 10 percent of participants relapsed. For patients who do see a recurrence of symptoms, several studies have found results suggesting that most patients will respond favorably if treated again using the same treatment parameters (Fitzgerald, Benitez, de Castella, Brown, Daskalakis, & Kulkarni, 2006). Electroconvulsive therapy (ECT), on the other hand, is associated with high rates of early relapse. In a meta-analysis of relapse rates in responders to an acute course of ECT administered for a major depressive episode, Jelovac, Kolshus, and McLoughlin (2013) examined thirty-two studies with up to 2 years' duration of follow-up. Where pharmacotherapy was continued following treatment, 51.1% of patients relapsed by 12 months following successful initial treatment with ECT, with the majority (37.7%) relapsing within the first 6 months. The 6-month relapse rate was similar in patients treated with continuation ECT (37.2%). In randomized controlled trials, they found that antidepressant medication halved the risk of relapse compared with placebo in the first 6 months. Thus, despite the continuation of ECT therapy, the risk of relapse within the first year following ECT is substantial, with the period of greatest risk being the first 6 months. Maintenance of well-being following successful ECT undoubtedly need to be improved.

Overall, TMS is well tolerated by patients. In fact, the discontinue rate is much lower than what is typically observed in other treatments, particularly medication trials.

For example, in the two large multisite rTMS trials, the drop out rate in the active groups were 12% and 10%; single site studies produced drop out rates averaging around 5% (O'Reardon et al., 2007; George et al., 2010). In their meta-analysis examining dropout rates in head-to-head medication trials for major depressive disorder, Machado, Iskedian, Ruiz, and Einarson (2006) found drop out rates of SNRIs, SSRIs, and TCAs at 26.1%, 28.4%, and 35.7% respectively. Side effects are marginal compared with pharmacology and include discomfort at the site of stimulation as well as headaches during and shortly following treatment. The risk of these side effects is greatly reduced with guidelines now stating that the procedure be prescribed by a physician and that stimulation parameters be individually established. In rare instances, seizures have also been reported. However, not only is the risk of seizure lower for rTMS as compared to ECT, safety studies of rTMS have also shown inhibition of the motor cortex after low-frequency stimulation. This finding suggests that such stimulation may actually be useful in suppressing the development and spread of epileptogenic activity. Patients who do experience a seizure, however, are generally not at an elevated risk of seizure than they were before (George, Lisanby, Avery, et al., 2010).

Although the overall safety of rTMS is reassuring, there are a few contraindications. For example, individuals with metal in their head, with the exception of their mouth, are not good candidates for rTMS due to the potential for metallic hardware being heated by the coil. Clinicians are also cautioned when considering rTMS for patients with cardiac pacemakers and implanted medications pumps to consult with the manufacturers of such devices. Compelling clinical reasons would also be necessary to treat children and pregnant women with rTMS. Finally, tricyclic antidepressants,

neuroleptic agents, and other drugs that lower the seizure threshold might be contraindications for rTMS. In each of these circumstances, a conscientious risk-benefit assessment must be conducted (Wasserman, 1998).

Epidemiology of Depression

According to the World Health Organization, affective disorders are the most debilitating and the most significant contributors to the total burden of disease worldwide (World Health Organization, 2001). The tremendous impact of depression is easily explained by its high prevalence, its early onset, its recurrent nature, and the impaired social and cognitive capabilities that result, thereby diminishing an individual's ability to adapt to life circumstances and to identify and obtain necessary resources (Miret, Ayuso,-Mateos, Sanchez-Moreno, & Vieta, 2013). The burden of depression is not easily resolved without efficient health systems and most importantly, available treatment strategies.

Depression affects an estimated 350 million individuals worldwide. The rates of depression swell during middle-to-late adolescence with gender differences emerging in adulthood. In fact, twice as many women experience depression as men (Hankin and Abramson, 2001). Within the United States, the lifetime prevalence is approximately 29.9% with a 12-month prevalence of about 8.6%. Not surprisingly, significant costs to patients, their families, caregivers, employers, and insurance payers ensue resulting in an estimated cost exceeding $80 billion each year in the United States alone. These costs, of course are associated not only with health care but also with suicide mortality and lost workplace productivity (Berry, Broglio, Bunker, Jayewardene, Olin, & Rush, 2013).

Of those affected by clinical depression, between 60 and 70 percent will respond

to pharmacotherapy, dispensed at the maximum dose. An additional 10 to 20 percent will improve following additional trials including first or second choice antidepressants. The remaining 10 to 15 percent of patients will not respond to drug therapy and will be classified as having treatment-resistant depression. This designation not only indicates that the patient has not experienced a full remission, but has also not seen a 50 percent reduction in depressive symptoms (Takahashi, Shirayama, Muneoka, Suzuki, Sato, & Hashimoto, 2013). Not surprisingly, a distinguishing characteristic of this subgroup is the common occurrence of suicidal thoughts, attempts, and in up to 10 percent of cases, completed suicides, making the discovery of efficacious treatment options critical (Ciprani, Girlanda, Agrimi, et al., 2013).

The primary treatment for TRD is electroconvulsive therapy (ECT). Due to the potential side effects, associated stigma, and unfavorable risk-benefit ratio, many patients with TRD will not elect to pursue ECT as a treatment option (Fava & Davidson, 1996). The bulk of rTMS research has been conducted with this patient group with outcomes suggesting that high-frequency stimulation applied to the DLPFC produced superior antidepressant effects compared to sham in numerous meta-analyses, including over 1000 randomized subjects (Slotema, Blom, Hoek, Sommer, 2010).

The discussion of TRD would be incomplete without a review of psychotherapeutic interventions. In fact, some have argued that a trial of cognitive-behavioral therapy by an experienced therapist should be performed before labeling an episode of major depression as refractory or treatment resistant. In support of this modification, Fava, Savron, Grandi, and Rafanelli (1997) examined nineteen patients who failed to respond to at least two trials of antidepressant drugs of adequate dosages

and duration who were then treated by cognitive-behavioral methods. Three of the patients dropped out of therapy, but the remaining 16 experienced a significant decrease in scores on the Clinical Interview for Depression after therapy. Twelve patients were judged to be in remission at the end of the trial and only one of these patients was found to have relapsed at a 2-year follow-up. Also in support of psychotherapy interventions for TRD, Thase, Friedman, and Howland (2001) have suggested that the efficacy of pharmacological interventions may be adversely affected by a poor therapeutic alliance, low social support, life stress, or chronic adversity and cognitive or personality factors such as neuroticism or pessimism. They review the literature suggesting that interpersonal, cognitive, and behavioral forms of psychotherapy have shown to address these complexities and should be considered as treatment options when pharmacotherapy fails to produce adequate treatment response. Finally, in their meta-analysis examining the treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations, Thase, Greenhouse, Frank, et al. (1997) found widespread support for combined therapy in more severe, recurrent depressions. Taken together, it can be argued that treatment resistant should apply only when a psychotherapeutic effort has been made. Until then, it may be more appropriate to define depression as "drug refractory" or "drug resistant".

Neurophysiology/Pathophysiology of Depression

Major depressive disorder is a complex, heterogeneous diagnosis characterized by a variety of neuroendocrine, neurochemical, neurophysiological, and neuromorphometric abnormalities. Its etiology is related to the interaction of genetics, adverse events in childhood, and ongoing and recent stress (Rot, Marije, Mathew, & Charney, 2009).

Elucidating the interplay among neurotransmitters and the related structural, functional, and psychosocial elements has been a major focus of research, especially with the advent of neuroimaging (Gotlib & Hamilton, 2008).

Initial investigations into the neurobiology of MDD focused almost entirely on the monoamine neurotransmitters serotonin (5-HT), norepinephrine (NE) and dopamine (DA). Research into these neurotransmitters resulted in the monoamine hypothesis, which has dominated the understanding of depression and driven pharmacological approaches to its management. The hypothesis asserts that depression results from a deficiency of monoamines at key sites in the brain (Van Praag, 2001). The hypothesis however is not without its shortcomings. For example, it cannot account for why two to three weeks of pharmacological interventions are required to resolve depressive symptoms despite the fact that the monoamine levels targeted by these drugs show increases in as few as one to two days. It also cannot explain the lack of antidepressant effects by illicit drugs like cocaine and amphetamine, which enhance these same neurotransmitters. Although most novel antidepressants reflect the claims of the monoamine hypothesis, it is being increasingly undermined and new biological models for understanding depression are now emerging. These new approaches have targeted dysfunction of the hypothalamic-pituitary-axis, the hypothalamic-pituitary-thyroid, second messenger pathways, calcium levels, and cytokines (Hindmarch, 2001). As the knowledge of the brain and depression increases, the increased understanding of these and other associated features will likely pave the path for novel antidepressants that might be superior to those currently available.

As new biological approaches to understanding depression continue to evolve,

molecular insights, and the monoamine hypothesis specifically, have been far from abandoned. In fact, Rot, Marije, Mathew, and Charney (2009) have offered a revised monoamine hypothesis suggesting that the role of serotonin should continue to be an ongoing research emphasis, although a new perspective may be necessary. For example, they assert that the low serotonin synthesis observed in depressed patients might not be the cause of depression as traditionally thought but rather, the result of depression and that a third variable, responsible for triggering depression, may actually be responsible for the reduced synthesis.

The role of serotonin in depression is also not fully understood without incorporating what is known about the genes that influence serotonin metabolism, particularly during times of stress. It cannot be argued that stress is a common precipitating factor for depression (Wurtman, 2005). Although no gene, or even a series of genes, have been identified as a cause for depression, the serotonin transporter gene is the most studied in MDD. It is of particular interest to scientists because it contains a polymorphism, a gene variation that my increase the risk for depression, that gives rise to two different alleles (long and short) that can occur in any combination. It is the short allele that slows down the synthesis of the serotonin transporter, which in turn, inhibits the speed that serotonin neurons can adapt to changes in their stimulation. Therefore, in support of a gene-environment interaction, it appears that carriers of the short allele of the serotonin transporter may be especially vulnerable to depression when faced with stress (Caspi, Sugden, Moffitt, Taylor, Craig, Harrington, McClay, Mill, Martin, Braithwaite, & Poulton, 2003). Other studies have built upon this finding and shown that serotonin is not the only gene interacting with the environment to create a risk for depression. For

example, Cicchett, Rogosch, Sturge-Apple (2007) examined child maltreatment and polymorphisms of the serontonin transporter and monoamine oxidase A (MAOA) genes in relation to depressive symptomatology. Findings did support a gene by environment interactions but heightened depressive symptoms were found only among extensively maltreated youth with low MAOA activity. Among comparably maltreated youth with high MAOA activity, self-coping strategies related to lower symptoms. Sexual abuse and the 5-HTT short/short genotype predicted higher depression, anxiety, and somatic symptoms, but again, this interactions was further moderated by MAOA activity level. Therefore, the interactive effects of multiple genes and psychosocial stress on the risk of depression will require further research (Cicchett, Rogosch, Sturge-Apple, 2007).

Norepinephrine, another neurotransmitter driving the monoamine hypothesis, has primarily been associated with the experience of stress whereby a threatening or novel stimulus evokes an increase in NE activity. In the context of MDD, depleted NE levels in response to prolonged or unresolved stress, dysregulate the mechanisms that would typically allow a return to homeostasis following this threat response. This dysregulation has been associated with cognitive symptoms such as hopelessness, helplessness, and guilt. Antidepressants targeting the reuptake of NE specifically have demonstrated comparable clinical efficacy to selective serotonin reuptake inhibitors (SSRIs) (Nemeroff, Entsuah, Benattia, Demitract, Sloan, & Thase, 2008).

Like serotonin and norepinephrine, dopamine is another neurotransmitter that is thought to play a critical role in the pathophysiology of MDD. Studies on it function in depression have observed that environmental threats perceived by the amygdala raise the level of dopamine in the prefrontal cortex as well as in the ventral striatum. As with

norepinephrine functioning, inhibitory feedback allows a return to homeostasis following a perceived threat. The possible lack of local inhibitory feedback in the striatal dopamine system may help explain why depressed patients often attribute inappropriate salience to even mildly negative stimuli (Dunlap & Nemeroff, 2007). Unlike serotonin and norepinephrine, there are currently no antidepressants that directly impact DA transmission. It has therefore been speculated that many patients with MDD might experience unremitted or residual symptoms, an especially important consideration when exploring treatment-resistant depression.

In addition to the molecular aspects of depression, the structural neurology of MDD also continues to evolve and guide treatment options. In fact, there is an entire sub-discipline of the biobehavioral sciences dedicated to clarifying the neural bases of mood and emotion known as affective neuroscience (Davidson, Pizzagalli, Nitschke, & Putnam, 2002). In response to the advanced neuroimaging techniques now available, key regions of the brain implicated in MDD are now being more precisely identified. Neuroscientists examining the emotional circuitry of depression have identified some consistent findings that point to certain anatomical abnormalities. Such abnormalities have been discovered in the limbic system, a complex of structures including the amygdala, hippocampus, subgenual anterior cingulate cortex (ACC), and hypothalamic-pituitary-adrenal axis. Cortical areas, namely the dorsolateral prefrontal cortex, also appear to play a prominent role in depression, particularly with emotion regulation and cognitive control (Davidson, Lewis, Alloy, Amaral, Bush, Cohen, Drevets, Farah, Kagan, McClelland, Noel-Hoeksema, & Peterson, 2002).

Studies of the amygdala demonstrate its involvement in emotionally mediated

attention, assigning emotional significance to stimuli and in remembering emotionally significant events (Gotlib & Hamilton, 2008). Studies have shown that there is an inverse relationship between amygdala volume and number of depressive episodes. Additionally, in studies using positron emission tomography (PET), elevated amygdala activity, cerebral blood flow (CBF), and metabolism, appear to be positively correlated with depressive severity (e.g., Drevets, Bogers, & Raichle, 2002). Another consistent finding suggests the presence of increased amygdala response to emotional stimuli. This is particularly true in response to negatively valenced stimuli (e.g., Sheline, Barch, Donnelly, Ollinger, Snyder, & Mintun, 2001). These patterns, while well documented, do not occur in all patients with MDD. Rather, these trends appear to be more prevalent in those who present with a high level of dispositional negative affect and anxiety (Davidson, Lewis, Alloy, et al., 2002). In fact, it has been speculated that the increased amygdalar activation in depression in general may also represent a possible biological substrate for anxiety, which is often comorbid with depression (Davidson, Pizzagalli, Nitschke, & Putnam, 2002).

In recent literature, the hippocampus, an area of the brain involved in episodic, declarative, contextual, and spatial learning and memory, has also become implicated in the expression of depression. Many forms of psychopathology, depression included, involve difficulty in the context-regulation of affect. In other words, mood and anxiety disorders can be characterized by the display of normative affective responses in inappropriate contexts. An example would be sadness that may be appropriate in the acute period following a loss but that persists for much longer. From this, some have hypothesized that the tendency towards the inappropriate context-regulation of affect in

depression may suggest hippocampal dysfunction. Recent morphometric studies have indeed reported hippocampal atrophy in patients with MDD. Inconsistencies do exist however and may relate to moderator variables that have not yet been identified or the possibility that hippocampal atrophy may be a symptom and not a cause of MDD (Davidson, Lewis, Alloy, et al., 2002).

Another limbic structure, the subgenual ACC is thought to mediate the subjective aspects of emotions and emotional responses to stimuli. Decreases in activity and volume for this brain structure are associated with depression (Drevets, Price, Simpson, Todd, Reich, Vannier, & Raichle, 1997). One especially interesting finding, concerning from the work of Siegle, Carter and Thase (2006), showed that individuals with depression, who respond favorably to cognitive behavioral therapy have less subgenual ACC response to affective words than do those who do not improve.

Other regions of the ACC have also been noted in patients with MDD. For example, it has been postulated that the hypoactivation observed in dorsal regions of the ACC in patients with depression might be associated with impaired modulation of attention or executive functions and impaired monitoring of competition among various response options. Further, the hypoactivation in ventral regions of the ACC may be associated with blunted conscious experience of affect, hypoarousal, anhedonia, reduced coping potential in situations characterized by uncertainty and conflict, and expectancy violations between the environment and one's affective state (Davidson, Pizzagalli, Nitscheke, Putnam, 2002). Finally, one study again pointing to the heterogeneity of depressive substrates and symptom expression found that a reduction of anxiety/somatization symptoms was associated with decreased activation in the ventral

ACC whereas improvements in psychomotor retardation symptoms were associated with increased activation in the dorsal ACC (Brody, Saxena, Mandelkern, Fairbanks, Ho, & Baxter, 2001).

Yet another consistent finding in the research on brain abnormalities in patients with MDD involves over-activity of the hypothalamic-pituitary-adrenal (HPA) axis, which is responsible for the neuroendocrine response to actual or perceived threats. In fact, it is one of the most replicated biological findings in major depression (Davidson, Lewis, Alloy, et al., 2002). There have been two hypotheses, which are not mutually exclusive that been offered as pathophysiological explanations for the HPA over-activity noted in depression. The first one points to the elevated levels of corticotropin-releasing factor (CRF) common to depression, stating that these increased levels drive the HPA axis into overdrive (Nemeroff, 1996). The second hypothesis suggests impaired negative feedback at both the pituitary corticotrope and central glucocorticoid receptor levels (Young, Hasket, Murphy-Weinburg, Watson, Akil, 1991).

Cortical structures have also become implicated in depression, namely the dorsolateral prefrontal cortex (DLPFC). The left DLPFC is an area of the brain responsible for maintaining the representation of goals and the means to achieve them. The right DLPFC however, is hypothesized to be particularly important to the maintenance of goals that require behavioral inhibition and withdrawal in situations that involve strong alternative response options. Compared to healthy individuals, studies have consistently demonstrated decreased activity during resting state (Mayberg, Lozano, Voon, McNeely, Seminowicz, Hamani, Schwalb, & Kennedy, 2005), during relapse (Bremner, Innis, Salomon, Staib, Ng, Miller, Bronen, Krystal, Duncan, Rich, Price,

Malison, Dey, Soufer, & Charney, 1997), and in response to affective stimuli in the DLPFC of depressed patients, predominantly on the left side (Hooley, Gruber, Scott, Hillner, & Yurgelun-Todd, 2005). In studies using electroencephalographic (EEG), asymmetric activation in anterior scalp regions of the DLPFC has been found showing reduced left relative to right activation in depressed and dysphoric individuals (Bell, Schwartz, Hardin, Baldwin, & Kline, 1998). Low levels of activity in the left DLPFC would help to explain the tendency for persons with depression to ruminate, reflecting the difficulties in cognitive control (e.g., Mayberg, Liotti, Brannan, McGinnis, Mahurin, Jerabek, Silva Tekell, Martin, Lancaster, & Fox, 1999).

The asymmetrical findings in the DLPFC for patients with depression also reveal some interesting discoveries specific to the right side. For example, Debener, Beauducel, Nessler, Brocke, Heilmann, & Kayser, (2000) recently confirmed earlier findings of greater relative right-sided frontal activation in depressed patients compared with controls. Another related finding suggests that among women in particular, SSRI treatment responders had significantly less relative right-sided activation compared with non-responders. Considering the role of right prefrontal regions in components of negative affect along with right posterior regions in arousal and anxiety, these findings imply that those subjects with global right-activation who would be expected to have symptoms of negative affect and anxious arousal are least likely to show improvements with SSRI treatment.

The picture that emerges from the investigations into the neurobiological aspects of depression is one that demonstrates certain trends, but not absolute consistency and homogeneity. Although neuroimaging studies have unearthed trends in regional cerebral

blood flow (CBF), volume, and glucose metabolism in the aforementioned areas, it is important to note that disagreements do exist regarding the specific locations and direction of these abnormalities. And, these structures are all interconnected in regionally specific ways, and so, feedback is also bidirectional. It is therefore still too early to tell which of the structural and/or functional abnormalities may be primary and which may be secondary. Depression is above all else, a complex, disorder with multiple subtypes and symptom profiles. Ongoing research will be necessary to more explicitly conceptualize depression and the specific neural, functional, and structural abnormalities associated with each. Parsing the heterogeneity of MDD on the basis of known brain circuitry is proving to be a promising approach to subtyping that relies more on the objective characterization of the specific affective deficits in patients with MDD and less on descriptive nosology. This ambitious effort could lead to the characterization of different endophenotypes that could then be used for genetic studies and more tailored treatment approaches.

Neurocognitive Impairments in Depression

Along with pervasive mood symptoms and anhedonia, MDD is characterized by disturbances in multiple domains including cognition. In fact, negative thought patterns, including pervasive and rigid negative views of the self, the world, and the future are core features of depression. Much like the neurocircuitry of depression however, the specific cognitive aspects of depression are not yet fully understood. What is known, points to two main types of cognitive abnormalities in MDD, cognitive biases and cognitive deficits, which provide evidence for the potential neurobiological correlates of each (Murrough, Iacoviello, Neumeister, Charney, Iosifescu, 2011).

Cognitive biases, a particularly common facet of depression, involve directed attention and memory towards negative themes in cognitive processing. Numerous studies have demonstrated particular biases primarily related to perception and attention, interpretation, and memory. Regarding perception, depressed individuals show preferential perception and processing of information towards negative as compared to positive or neutral information (Gotlib and Joorman, 2010). Similarly, it appears that when interpreting information, depressed individuals tend to make stable, global, and generally negative inferences for the causes and consequences of life events (Fresco, Heimberg, Abramowitz, & Bertram, 2006). Finally, as it pertains to memory, studies have shown that depressed individuals are less able to expel irrelevant negative information from working memory than their non-depressed counterparts. They also appear to be more impaired at identifying positive content in the context of representations competing for resources in working memory (Levens & Gotlib, 2009). Despite these findings, and the gains made in characterizing the negative biases of depression, their specific role is far from clear. And like many other factors associated with MDD, the question regarding which is the predecessor, negative biases or depressed mood, remains unanswered.

Coupled with the research gains made in documenting the aspects of negative processing bias in depression, research has also focused on the deficits in cognitive functioning unrelated to emotional processing. Much like the expression of cognitive biases, the domains most commonly documented in the literature are attention, executive functioning, and memory. Deficits in these domains are consistently documented and similar in both vegetative and depressive subtypes (Herrera-Guzman, I., Gudayol-Ferre,

E., Jarne-Esparcia, A, et al, 2009). It is believed that the deficits noted across these two groups are due to the reduced metabolic activity within dorsal regions of the prefrontal cortex in combination with the elevated limbic activity in MDD (Murrough, Iacoviell, Neumeister, Charney, Iosifescu, 2011).

Although they are not mutually exclusive and the tasks used to measure cognitive domains have considerable overlap, there is enough distinction to discuss them separately. Executive function, which is known to originate in the anterior regions of the brain, encompasses judgment, planning, abstract thinking, metacognition, cognitive flexibility, inhibition, verbal fluency, initiative, and the ability to direct behavior in a goal-directed fashion (Levin, Heller, Mohanty, Herrington, & Miller, 2007). Impairments across these facets of executive function have been demonstrated in individuals with depression. Despite this, a clear pattern of impairment with regard to subtype of depression, severity, or medication status has not been identified. This might be due to the multiple strategies that can be used to perform these tasks and the comorbidity of depression and anxiety (Rogers, Kasai, Koji, Fududa, Iwanami, Nakagome, Fukuda, & Kato, 2004).

The neural physiology of depression helps bolster what is known about the executive functions common in MDD. The majority of studies have demonstrated that elevated activity in a brain region is linked to increased performance on tasks specialized to that region (Heller, Kitschke, Etienne, & Miller, 1997). As already addressed, there is an asymmetry of the frontal lobe with decreased activity in the left dorsolateral prefrontal cortex. On a broad level, the left prefrontal cortex appears to be associated with many of the deficits seen in depression including, but not limited to, the capacity to construct

meaning and generate inferences that extend beyond the information presented, strategizing, initiation, and self-cuing (Banich, 2004). The distinct functions associated with the right prefrontal cortex are less understood. However, preliminary neuroimaging has suggested that inhibitory control, the suppression of unwanted memories, and involvement in the threat-response network are specialized functions of this region. There are a limited number of studies that have specifically investigated the relationship between the hyperactivity of the right dorsolateral prefrontal cortex and the regionally specialized tasks in MDD. It has been hypothesized however, that such studies will display deficits that correspond with the elevated activity and the specialized tasks associated with this region (Nitschke, Heller, & Miller, 2000).

Along with impairments in executive function, there are a number of memory deficits that have been demonstrated in patients with depression including problems with autobiographical remembering, episodic memory recall, and working memory (Levin, Heller, Mohanty, Herrington, & Miller, 2007). The association between depression and memory has been identified as quite stable in a meta-analysis examining 147 recall and recognition studies in clinically depressed and non-depressed samples. In this same review, two particular findings emerged: deficits with explicit memory tasks were more pronounced than implicit tasks and patients with MDD have a propensity to remember negative material better than positive material (Burt, Zembar, & Niederehe, 1995).

Although memory deficits are well documented in persons with depression, the reasons for this trend in depression are a bit less clear. One hypothesis argues that the deficits in executive function may be partly responsible. Heller and Nitschke (1997) proposed this possibility in response to the finding that depression limits the ability to

initiate the cognitive strategies that enhance an individual's ability to process and remember information. Another theory has to do with attentional control strategies, which are underutilized in person's with depression. In studies where these strategies are specifically treated through focusing and relevance strategies, memory deficits in depression have been observed (Hertel, 1994). Finally, abilities to efficiently encode information and lack of engagement with effortful memory strategies might help to explain these particular cognitive deficits.

The memory deficits inherent to MDD have also prompted researchers to begin investigating the hippocampal abnormalities associated with the disorder. These studies have focused on hippocampal volume however and have not yet targeted how hippocampal function is specifically related to cognitive ability. It is expected however that research exploring the intersection of the affective and cognitive aspects of subcortical regions will soon ensue (Levin, Heller, Mohanty, Herrington, & Miller, 2007).

Along with deficits in executive function and memory, impaired attention is another cardinal feature of depression. In fact, one of the cognitive criteria for the diagnosis of depression in the DSM-IV-TR is decreased concentration. Not only is attention a prominent feature of depressive episodes, but problems with sustained attention have also been evidenced as an ongoing problem even during periods of symptom remission (Weiland-Fiedler, Erickson, Waldeck, Luckenbaugh, Pike, Bonne, Charney, & Neumeister, 2004).

As with memory, it appears that many of the attentional deficits observed in depression may result from impairments in executive function. Individuals with MDD

often show an impaired ability to suppress external and internal distractors, which in turn, leads to an insufficient allocation of resources. Evidence for this difficulty in persons with depression stems from performance on attentional tasks, which require distractor inhibition, such as the color-word Stroop task (Levin, Heller, Mohanty, Herrington, & Miller, 2007). Deficits in attentional processing in depression have also been demonstrated with event-related brain potential (ERP) studies. The results from such studies suggest that difficulties with attention are not merely the result of diminished motivation (Fernandes et al., 1999; Keller et al., 1999).

The cognitive performance associated with depression is yet another reminder of its diverse etiologies and manifestations. Despite the vast number of genetic and environmental configurations, depression does appear to affect similar brain regions and the functions associated with these cortical and subcortical areas. Therefore, while the discovery of consistent patterns of relationships among specific cognitive impairments and specific brain region activity is not yet clear, affective neuroscience is proving that continued research efforts are paying off. With continued exploration into the cognitive deficits associated with depression and its various subtypes, the search for respective treatment methods that can ameliorate depression becomes more and more promising.

Effect of TMS on Depression Mechanisms

The efficacy of both high-frequency (HF) and low-frequency (LF) rTMS for depression have been well documented although the underlying mechanisms are not yet fully understood. The bulk of existing studies have focused on HF application to the left dorsolateral prefrontal cortex (DLPFC). This type of stimulation has been shown to produce greater antidepressant effects than sham in multiple meta-analyses, including

more than 1000 randomized subjects (Schutter, 2009; Slotema, Blom, Hoek, et al., 2010).

Like HF applications, LF rTMS applied to the right DLPFC and supplemental motor area has also been evaluated in a number of trials with promising results. In fact, it has been found to be efficacious when evaluated alone and in all comparative trials, it has been shown to share equal antidepressant effects with HF, left-sided treatments (Fitzgerald & Daskalakis, 2012). At present, one meta-analysis exists confirming the efficacy of right-sided treatments for depression (Schutter, 2010).

The bulk of findings related to the antidepressant mechanisms of rTMS stem from animal studies. Such studies have demonstrated effects of rTMS on dopaminergic neurotransmission, a neural substrate of depression previously discussed. Elevated dopamine concentrations have been found in multiple brain regions following both HF and LF treatments. Coupled with increased dopamine, these same studies observed increased extracellular glutamate in the same regions (Padberg & George, 2009). Despite this and other studies that have found an effect of rTMS on the neurotransmitter systems involved in the pathophysiology of MDD, the comparison to prefrontal rTMS is a bit controversial in humans given the functional anatomical differences in men and rodents. In a recent study however, Strafella, Paus, Barrett, and Dagher (2001), did observe an induction of dopamine release in the caudate nucleus of healthy volunteers following rTMS.

As discussed earlier, two consistent findings reported in the MDD neuroimaging literature are the metabolic hypoactivity in the left DLPFC and hyperactivity in the right DLPFC, areas, which are interconnected to the brain circuits involved in cognitive and emotion regulation (Schutter, 2009, Juckel et al., 1999). Thus, it has been proposed that

stimulating neuronal activity in these brain region will, in turn, exert indirect effects on underlying interconnected brain regions and will result in antidepressant effects (Juckel et al., 1999). The DLPFC is anatomically situated on the surface of the cortex, making it a highly conductive brain region for exteriorly applied stimulation (the TMS coil is able to emit magnetic field pulses through the cranium that remain sufficiently strong for approximately 2-3 centimeters deep). Again, TMS produces an electrical field that induces neuronal depolarization that then initiates an action potential. It is this action potential that ignites an excitation of neuronal activity. "Repetitive" TMS is utilized to achieve sustained modulatory effects. It is this rationale that has been proposed as the explanation for the documented antidepressant resulting from rTMS treatment. However, an explanation of the exact mechanism of action driving these effects has not yet been completely determined.

Although cerebral blood flow (CBF) abnormalities are a consistent finding in the MDD research, there appears to be an asymmetry in the DLPFC, with reduced flow on the left and increased flow on the right. rTMS addresses this heterogeneity as high-frequency application enhances cerebral blood flow to the left and low-frequency application inhibits cerebral blood flow on the right. In fact, in their study investigating changes in blood flow following low-frequency right prefrontal stimulation (LFRS), Kito, Hasegawa, & Koga (2011), found that the therapeutic efficacy of LFRS was correlated with decreases in CBF not only in the right prefrontal cortex, but also in the bilateral orbitofrontal cortex, right subgenual cingulate cortex, right putamen, and right anterior insula. ECT on the other hand has not been shown to improve upon the cerebral blood flow abnormalities associated with MDD. For example, Nobler, Sackeim, Prohovnik,

Moeller, Mukherjee, Schnur, Prudic, and Devanand (1994) found that global and regional deficits in cerebral blood flow and glucose metabolism were not reversed by successful treatment with ECT. In fact, in their study, ECT resulted in additional perfusion reductions.

Although the antidepressant efficacy of rTMS for MDD has been repeatedly demonstrated, the neuromechanisms implicated in this effect are not fully understood and thus, more research is required. However, for now, there is strong research support for the emotional and behavioral consequences associated with its application in patients with MDD and what is known about the mechanisms of action for this does parallel the known neural substrates of depression.

TMS and Neurocognitive Changes in Depression

The negative impacts on cognitive performance have been the major criticism of the treatment methods typically used for depression. As already discussed, ECT has been associated with both subjective and objective memory impairments. And, even when successfully treated with modern antidepressants, patients tend to be better cognitively than untreated patients, but they do not perform better than healthy comparison subjects (Gualtier, Johnson, & Benedict, 2006). What makes rTMS so appealing, in addition to its proven efficacy for treatment resistant depression, are the number of studies that show that in modulating cortical networks, enhancements in cognitive performance result.

Cognitive enhancement has been defined as any augmentation of the core information processing systems in the brain, including mechanisms underlying perception, attention, conceptualization, memory, reasoning, and motor performance (Luber & Lisanby, 2013). Beginning with healthy individuals, studies investigating the

neurocognitive consequences of TMS and rTMS focused on domains including attention, memory, executive functioning, and motor processing. Across these studies, no adverse neurocognitive effects were observed and to the contrary, a trend towards enhanced functioning emerged (Bridgers and Delancy, 1998; Hufnagel et al., 1993; Pascual-Leone et al., 1993; Wasserman, 1998; Jahanshahi et al., 1997).

Studies evaluating the neurocognitive effects of TMS in the treatment of depression have produced similar results, despite varying stimulation parameters (Little et al., 2000; Speer et al., 2001; Avery et al., 1999; Padberg et al., 1999; Triggs et al., 1999; Loo et al., 2001). This is especially promising as the use of rTMS in depressed populations typically involves longer exposure and more aggressive stimulation parameters and because as compared to healthy volunteers, patients with depression typically present with state-dependent cognitive dysfunction (Martis et al., 2003). As the evidence mounts concerning the lack of adverse effects resulting from rTMS treatment, the precise neurocognitive changes remain unclear and require additional systematic study. Results of previous research in this area are discussed below.

In their study on the cognitive effects of a 10-day trail of both low and high-frequency rTMS administered to the left PFC, Little et al. (2000) looked specifically at verbal learning, memory and fluency abilities. Results suggested no adverse cognitive effects and in fact, demonstrated gains in list recall after one week as compared to baseline. Using similar parameters over a 2-week trail, Speer et al. (2001) also found no decrease in scores and a "trend" suggesting improvements in verbal fluency. In a study utilizing 5 session of TMS administered to older adults, Moser et al. (2002) found significant improvements in executive functioning abilities (Trail Making Test-B). And

after only 5 days of rTMS, Padberg et al. (1999) demonstrated verbal memory improvements using both high and low frequency rTMS to the left PFC. Using the same stimulation site and high frequency (20Hz) rTMS, Triggs et al. (1999) found elevated scores on test of executive functioning and attention after 10 days. Finally, in a study using high frequency to the left PFC, Bayan (2013) found significant improvements in executive function, complex attention, and cognitive flexibility following 30 days of rTMS.

In one particularly interesting studying comparing the neurocognitive effects of unilateral ECT and rTMS in 30 treatment-resistant depression, Schulze-Rauschenbach et al. (2005), produced results favoring rTMS. Specifically, the rTMS group demonstrated improved cognitive performance and subjective memory complaints while the ECT group displayed deficits in anterograde and retrograde memory as well as ongoing subjective memory complaints. The incorporation of a healthy volunteer control group helped to minimize the potential for practice effects in this study.

It seems as though the potential adverse effects of rTMS on neurocognitive function are benign, and that there may even be some neurocognitive improvement resulting from this treatment for MDD, at least for left-sided treatments. Nevertheless, it is vital to continue investigating how different and potentially more effective stimulation parameters, including stimulation site, may affect the occurrence of cognitive side effects. After considering left-sided treatments from 6 open and 24 controlled studies from 1999 to 2009, Guse, Faliki, & Wobrock (2010) concluded that certain sub-domains of executive functioning seem to exhibit the greatest improvement including working memory, cognitive flexibility, and verbal fluency/retrieval. However, standardization of

treatment parameters across the studies reviewing was lacking, possibly explaining the variability across neurocognitive domain improvement in the studies reviewed. Furthermore, the vast majority of studies using rTMS have yet to evaluate the impact of neurocognitive change following right-sided applications, thereby warranting further investigation.

Study Rationale Conclusions and Hypotheses

Depression is a prevalent, disabling, and often, chronic psychiatric condition. More than 30% of those affected will not experience remission in response to traditional treatments, namely pharmacology. This treatment-resistant cohort has historically been left with limited treatment options. For this reason, different brain stimulation methods have received considerable research attention throughout recent decades. The oldest of these methods, electroconvulsive therapy, is considered an effective antidepressant for the acute intervention of treatment-resistant depression. It is however, invasive, not-easily tolerated, and has been linked to significant cognitive side effects. rTMS is now emerging as a treatment modality with equal efficacy for treatment resistant depression. Unlike ECT however, rTMS is safe, non-invasive, and has been linked with neurocognitive improvements.

An emerging theme from the literature on the neurobiological aspects of depression is the unresolved question regarding the possibility that the cognitive aspects of the disorder represent a separate dimension of the illness rather than being attributable to the core mood symptoms alone. Providing support for their distinctness, are the longitudinal studies that illustrate a subset of MDD subjects whose cognitive deficits persist, especially in the areas of sustained attention, verbal learning and memory, and

executive functioning, even when depressive symptoms have improved (Fava, Graves, Benazzi, Scalia, Iosifescu, Alpert, & Papakostas, 2006). Therefore, it is essential to continue the quest to delineate the aspects of depression, particularly the cognitive dysfunction that may result in poor psychosocial functioning, and may persist beyond certain symptom remission. Clarity in this regard may justify specific treatment strategies aimed at the cognitive and functional deficits in these patients (Murrough et al., 2011). rTMS is particularly promising as it's electromagnetic stimulation of neurons capitalizes on neuroplasticity to induce lasting neuronal change within multiple brain regions. Thus, rTMS carries not only the promise of addressing the neural substrates responsible for the affective experience of depression, but the possibility of targeting the neurobiological basis of the neurocognitive deficits as well. Preliminary studies have begun to provide evidence for this latter possibility, though treatment parameters are varied, with many studies utilizing stimulation parameters below what has been recommended and have assessed neuropsychological performance with paper and pencil tests alone. In this study, an entire course of treatment was completed using the recommended dose of rTMS (35 sessions of 1,200 pulses @ 1Hz, 110% to the RDLPFC and 1,200 pulses @ 1 Hz, 100% to the SMA). The stimulations were delivered in 1-second pulses each and neuropsychological testing utilized computerized administration, enhancing standardization. This study was also one of the first to investigate the neurocognitive changes associated rTMS administration to the RDLPFC and SMA.

Research Questions

1. Are there statistically significant differences in neurocognitive scores following 2 and/or 6 weeks of rTMS treatment as compared to pre-treatment?

2. If significant improvements in neurocognitive scores are found, do these improvements occur independent of a reduction in depression scores?

Discussion of Possible Outcomes

This study aimed to assess the impact of approximately 35 sessions of low-frequency rTMS on neurocognitive functioning in the treatment of treatment-resistant depression. The current study hypothesized that when low-frequency rTMS was applied to the right DLPFC as well as to the supplementary motor area, significant improvements in executive functioning, complex attention, and cognitive flexibility scores, as measured by CNS Vital Signs (computer-based test battery), from pre-treatment to post-treatment would be observed. Furthermore, it was hypothesized that improvements in neurocognitive scores would be evidenced after the initial 2 weeks of treatment with continued improvements in scores at post-treatment (Hypothesis 1A). It was believed, based on the findings of previous studies, that improvements would take place independent of improvements in clinical depression and anxiety scores, as measured by the BDI-II and the BAI (Hypothesis 1B). Stated differently, neurocognitive score improvements would be evidenced independent of mood improvement, suggesting mechanisms of change in cognition via neuronal activation in the DLPFC versus improvement in mood alone. If these hypotheses are upheld, it will further validate rTMS as a non-invasive and effective treatment alternative to ECT that offers neurocognitive benefit versus neurocognitive impairment.

In the event that these hypotheses were not upheld, several explanations could have been applicable, beginning with methodological limitations. The very limitations of subject enrollment itself in TMS studies and patients in TMS treatment programs (e.g.,

financial, time commitment, unfamiliarity with the treatment, etc.), could have impacted the results, leading to non-significant neurocognitive pre- to post-treatment score improvements or changes due to small sample size and low statistical power. These same factors may have also caused sample bias and limited the study sample demographic (e.g., higher socioeconomic status, higher education levels, older in age). If however the subjects had varied vastly in age, discomfort with the use of computers for the older subjects may have led to confounded results. Another potential restriction was the computer-based test battery used in the study, CNS Vital Signs, which may have lacked adequate sensitivity to assess the construct of interest (i.e., neurocognitive functioning) in a clinical population over time. Improvements in neurocognition might also have been explained by a correlation that exists between improvement in mood scores and improvement in neurocognition. In other words, if results had revealed that neurocognitive improvement did not exist independent of mood changes, then it could have been expected that a lack of significant change in mood scores would illicit no significant change in neurocognition. A lack of controlled circumstances for subjects undergoing rTMS treatment may have also confounded the results. Such circumstances included differences in supplemental treatments for depression (e.g., medications, psychotherapy), adherence to the rTMS treatment schedule, severity of depression at baseline, and severity of neurocognitive impairment at baseline.

It was also possible that if non-significant findings were revealed, it may have been due in part to the stimulation parameters themselves. In the bulk of studies illustrating significant improvement in cognitive functions, a left-sided treatment has been used. This study was one of the first to explore cognitive change in response to

right-sided protocols, which involve two stimulation sites, the right dorsolateral prefrontal cortex (RDLPFC) and the supplementary motor area (SMA). As compared to left-sided treatments which typically involve 3,000 pulses administered at 120% of the established motor threshold to a single site and a stimulation time of 4 seconds given at intervals of 26 seconds, this study included the following: 1,200 pulses @ 1Hz, 110% of motor threshold (MT) administered to RDLPFC and 1,200 pulses @ 1Hz, 100% MT administered to the SMA.

CHAPTER II

METHODS

Participants

Data were derived from a larger study led by Serina Neumann, PhD., Associate Professor of Psychiatry and Behavioral Sciences at Eastern Virginia Medial School (EVMS). The study protocol was approved by the Institutional Review Board of EVMS on August 24, 2010 (IRB#: 10-07-FB-0135-EVMS). The purpose of this larger study is to establish a registry, or data bank, with information routinely employed in clinical practice on patients receiving TMS for the treatment of cognitive, emotional, and behavioral disorders (e.g. Major Depressive Disorder, Obsessive Compulsive Disorder, and Post Traumatic Stress Disorder) in humans. These data will serve to elucidate factors that may optimize or hinder the effectiveness of TMS in the treatment of these disorders. As a part of the broader treatment trial, all patients underwent neurocognitive testing via CNS Vital Signs to monitor neurocognitive changes associated with TMS treatment. rTMS and TMS treatment eligibility inclusion criteria for participants in the current study were as follows: 1) between the ages of 18 and 89; 2)DSM-IV diagnosis of MDD (determined by symptom review in the clinical interview and Beck Depression Inventory (BDI-II) score of $\geq$ 16); and 3) failed at least one antidepressant medication trail in the past at or above the minimal effective dose and duration in the current episode. TMS treatment eligibility exclusion criteria for participants in the current study were as follows: 1) currently suicidal; 2) currently pregnant (as determined via blood test); 3) seizure risk: history of seizure disorder, disease or injury that increases seizure risk (e.g. serious heart disease, increased intracranial pressure due to acute large infection or

trauma), family history of epilepsy, currently on medications that might increase seizure risk; 4) implanted electrodes or devices in the body or head; 5) skull defects; 6) tinnitus; 7) psychotic features; 8) currently taking Wellbutrin and disinclined to discontinue; and 9) any other contraindications for rTMS. Along with the clinical interview, medical records and clinical measures were reviewed to determine the above inclusion and exclusion criteria.

Procedures

Recruitment. TMS patients were recruited via referral from various clinicians in the surrounding community as well as clinicians within the Eastern Virginia Medical School (EVMS) Department of Psychiatry group. Each referred patient initially underwent an initial intake with the study coordinator to screen for any obvious contraindications and diagnostic appropriateness. If patients were determined to be eligible, they then underwent two clinical evaluations. A psychiatrist provided an initial interview aimed at evaluating treatment suitability, obtained a brief psychiatric history, and gathered a thorough psychiatric medication history. A licensed psychologist then conducted the second evaluation obtaining a more in-depth psychiatric history and assessment of symptoms. Once cleared (i.e., all eligibility criteria outlined in *Participants* section met) and deemed medically appropriate, the frequency and duration of treatment for each individual patient was determined by both clinicians and prescribed by a board-certified psychiatrist.

Setting. TMS treatment and assessments take place at EVMS, Psychiatry and Behavioral Sciences.

Administration of treatment and assessments. Once they were deemed eligible via clinical evaluations, treatment parameters for individual participants were prescribed by a board-certified psychiatrist. For depression, treatment was prescribed five days per week for 6 weeks (approximately 40 minutes per session) and 3 weeks of subsequent tapering (e.g., 3 TMS sessions during the 7rd week, 2 during the 8th week, and 1 during the 9th week).

Prior to beginning TMS treatment, clinical and registry consents were discussed and signed. Consent forms that outlined the registry study and TMS treatment purpose, procedures, risks, and benefit, were provided to each patient who was then asked to indicate their willingness to participate. Thereafter, patients underwent neurocognitive and psychological testing in order to ascertain baseline values. For the purposes of this study, the BDI-II and the BAI were the only psychological assessment measures examined. Neurocognitive functioning was assessed using CNS Vital Signs, a computer-based neurocognitive assessment battery. Neurocognitive and psychological assessments took place at 3 different time points throughout the trial (baseline, 2 weeks after starting treatment, and at the end of treatment), with each neurocognitive testing session taking approximately 25 to 30 minutes.

Prior to the initial TMS treatment session, the patient's resting motor threshold was established (RMT). This ensured precision of stimulation intensity as motor threshold can vary depending on factors such as age, gender, and cortical excitability (Lisanby, S. H. et al., 2002; Wassermann, E. M., 1998). RMTs were determined by applying a single magnetic pulse over the right motor cortex region, which stimulates a slight twitch in the contralateral hand. Magnetic pulses were applied in this fashion until

a slight twitch in the contralateral thumb was achieved. The intensity of stimulation was set at a maximum of 110% for the RDLPFC and 100 % for the SMA. Magnetic field intensity for each patient's resting motor threshold was calculated by the NeuroStar software. The coordinates of the resting motor threshold (RMT) and stimulation site, as well as the chair positioning parameters, were recorded using a positioning system to ensure reliable repositioning upon subsequent treatment sessions. Once stimulation intensity was determined, the exact site of stimulation was located and the coil moved accordingly. The two stimulation sites for this study were the right DLPFC, which is located approximately 5 cm anterior to the pre-central gyrus or motor strip, and the supplementary motor cortex which is located approximately 2 cm anterior to the pre-central gyrus or motor strip. Each treatment session consisted of 1,200 pulses @ 1Hz, 110% to the RDLPFC and 1,200 pulses @ 1 Hz, 100% to the SMA. The stimulations were delivered in 1-second pulses each.

Materials

Beck Depression Inventory-II (BDI-II). For this study depression was assessed using the BDI-II (Beck, Steer, & Brown, 1996). The Beck Depression Inventory-II is the most recent revision of a test with more than 35 years of nearly universal use. It was released in 1996 with the purpose of detecting the presence of depression in normal populations as well as the severity of depression in diagnosed patients for both adults and adolescents over the age of 13 (Arbisi, 1996). The measure consists of 21 items, each item made up of 4 statements organized in increasing severity rated on a 0-3 scale. The summary scores range from 0 to 63, with higher scores indicated higher levels of depression over the past week. During its development, considerable attention was given

to its ability to assess symptoms that correspond to the criteria listed in the DSM-IV for diagnosing depressive disorders. The psychometric properties of the BDI-II are quite good. Regarding internal consistency, coefficient alpha for the normative samples were as follows: outpatient sample = .92; college sample = .93. This was a notable improvement over the BDI-IA, which had an alpha coefficient of .83. On a related note, the test-retest reliability has been reported in the BDI-II at .93 ($p < .001$) (Beck, Steer, & Brown, 1996).

Beck Anxiety Inventory (BAI). For this study, anxiety was assessed using the BAI, which was released in 1988 by Beck, Epstein, Brown, and Steer. It was designed as a measure of anxiety, one of the most common complaints by patients seeking mental health treatment. It is a 21-item self-report measure that was created to assess solely anxiety, and not depression. The BAI was developed using questions from the following three measures, all of which were authored or coauthored by Beck: the Anxiety Check List (ACL), the Physician's Desk Reference Check List (PDR), and the Situational Anxiety Checklist (SAC). The 21 questions on the BAI examined the following anxiety symptoms: numbness/tingling, hot sensations, wobbly legs, inability to relax, fear of the worst, dizziness/lightheadedness, heart pounding, unsteadiness, terrified feelings, nervousness, feeling of choking, trembling hands, shakiness, fear of losing control, breathing difficulty, fear of dying, feeling scared, indigestion or stomach discomfort, feeling faint, flushed face, and sweating (due to something other than heat) (Beck & Steer, 1987). In his *Review of the Beck Anxiety Inventory* (2010), Dowd praised the measure for having excellent internal consistency reliability coefficients (ranges .84 to .95). Test-retest reliability over one week showed a coefficient of .75 and appears to be

stable over a one-month period (Beck, Epstein, Brown, & Steer, 1988). Regarding content validity, the BAI was created with the *DSM-III-R* symptom criteria as a guideline; mostly notable symptoms of Generalized Anxiety Disorder and Panic Disorder were used in this measure. Concurrent validity correlation coefficients ranged from .51 to .58 across multiple studies, so Beck and Steer concluded that the correlational magnitudes "demonstrate that the BAI is not only significantly but also substantially related to other accepted measures of both self-reported and clinically rated anxiety" (Beck & Steer, 1987).

CNS Vital Signs. CNS Vital Signs, a 30-minute, self-administered, computer-based battery, was used to assess neurocognitive performance. Studies have produced support for strong reliability with test-retest coefficients ranging from 0.65 to 0.88. Concurrent validity comparing CNS Vital Signs battery to conventional tests has been determined (Gualtieri, Johnson & Benedict, 2006). In a 2013 study by Bayan, practice effects for this battery were explored using non-clinical and clinical samples. Significant improvements in executive function, complex attention, and cognitive flexibility were observed in the clinical sample only, suggesting that changes can be attributed to treatment factors and not practice effects.

Seven conventional neuropsychological tests that span across cognitive domains that are sensitive to most causes of cognitive dysfunction and which are known to be reliable and valid comprise the CNS Vital Signs battery (Gualtieri & Johnson, 2006). These include: Visual Memory (visual learning and memory), Verbal Memory (verbal learning and memory), Finger Tapping (motor speed), Symbol Digit Coding (information processing and visual-perceptual speed), Stroop Test (executive function), Shifting

Attention Test (executive function), Continuous Performance Test (sustained attention). From these 7 tests, domain scores in the following 10 categories are produced: Neurocognition Index (NCI), Composite Memory, Verbal Memory, Visual Memory, Processing Speed, Executive Function, Psychomotor Speed, Reaction Time, Complex Attention, and Cognitive Flexibility.

Because this study aimed to evaluate domain scores for functions associated with the prefrontal cortex, only the following were inspected: Executive Function, Cognitive Flexibility, and Complex Attention. With the targeted sites of magnetic stimulation in mind, prefrontal cortex functions were hypothesized to be the most robustly affected by TMS treatment for depressed patients.

Executive Function tests measure one's ability to recognize rules, categories, and manage rapid decision-making. This predicts how well an individual can sequence tasks, multi-task, and track and respond to a set of instructions. *Cognitive Flexibility* tests capture the ability to adapt to a rapidly changing set of directions that progressively increases in complexity. This ability is relevant to decision-making, reasoning, planning, behavioral inhibition, and attentional abilities. *Complex Attention* tests measure accurate and rapid vigilance as well as the ability to attend and respond to information for an extended amount of time. This ability is relevant to exercising behavioral control. All domain scores are reflected as raw scores, which are then converted to a standard score for age (mean score is 100; standard deviation is 15).

As already discussed, the tests and test descriptions that form the above aggregate domain scores are as follows: 1.) *Symbol Digit Coding*: serial presentations of screens, each containing a row of 8 symbols with corresponding numbers, and a second row of 8

symbols with empty boxes below. The test taker is to type in the number that corresponds with the symbol that is highlighted, 2.) *Stroop Test*: comprising of three parts: first, pressing the space bar when the word appears on the screen; second, pressing the space bar when the color of the word matches the word; third, pressing the space bar when the color of the word does not match the word, 3.) *Shifting Attention Test: s*hifting from one instruction set to the next quickly and accurately by matching geometric objects by color or shape, and 4.) *Continuous Performance Test*: responding to a target stimulus presented on the screen, but not to any other stimulus presented.

Design and Statistical Analysis

For this study, using a Repeated Measures design, the neurocognitive effects of TMS in the treatment of depression were evaluated over time. The repeated measures factor was the neurocognitive assessments scores over three different time points (pre-treatment, 2 weeks, post-treatment) for patients receiving TMS treatment on the RDLPFC and SMA for MDD. An a priori power analysis was conducted to calculate the necessary sample size. For this investigation, the alpha level, or Type 1 error rate, was set to a standard .05. Statistical power was set to .8. At these specifications, it was determined that a sample size of seven would be necessary to detect a Cohen's d of .25 (partial η^2 = .577). Outlined below are the statistical analyses associated with each research question listed above:

1. A. Are there statistically significant differences in neurocognitive scores following 2 and/or 6 weeks of rTMS treatment as compared to pre-treatment? Three separate analyses were conducted, one for each cognitive domain (i.e., Executive Functioning, Complex Attention, Cognitive Flexibility) with

repeated measures analysis of variance (ANOVA) comparing pre-treatment, 2 weeks of treatment, and post-treatment scores. Pearson correlations were conducted to identify statistically significant potential covariates (e.g. BDI-II and BAI baseline scores and score change, number of sessions, age, sex, education level, and marital status) to be added to each analysis. Post-hoc Tukey's HSD analyses were used to elucidate any significant differences observed.

B. If significant improvements in neurocognitive scores are found, do these improvements occur independent of a reduction in depression and anxiety scores? In order to distinguish between neurocognitive changes attributed to TMS alone versus changes attributed to clinical improvement, six independent correlational analyses were conducted assessing the relationship between neurocognitive score change and both depression and anxiety score change.

CHAPTER III

RESULTS

Sample Demographics

In order to characterize the sample, descriptive statistics were conducted for the rTMS treatment group. Twenty total patients completed a course of rTMS for the treatment of treatment-resistant depression. As seen on Table 1, the total mean age of the 20 patients was 42.35 with a standard deviation of 12.50 and comprised of primarily females (25% males, 75% female) and those of Caucasian background (5% Asian, 5% African American, 90% Caucasian). Patient education level fell between completion of general education development (GED) and a master's degree with the 50% of the sample (N=10) achieving a bachelor's or master's degree. All patients met DSM-IV criteria for Major Depressive Disorder, with minimum number of years suffering from depressive/anxious symptoms being 2 years, maximum number of years being 30 years, and a standard deviation of 8.46 years. Number of rTMS treatment sessions varied according to multiple factors including treatment response and insurance allotment. Treatment continuation was based on factors assessing clinical response, such as BDI-II score decrease, subjective report by the patient, and clinical judgment by the study psychiatrist and psychologist.

Table 1

rTMS Group Demographic Data

	Min	*Max*	*M*	*SD*
Age	19	59	42.35	12.50
Number of years suffering from Symptoms	2	30	17.15	8.46
Baseline BAI Score	10	42	26.55	9.34
Baseline BDI-II Score	18	56	40.75	9.37
Total Number of Sessions	16	38	34.95	4.61
	N	*%*		
Gender				
Male	5	25		
Female	15	75		
Ethnicity				
Caucasian	18	90		
Asian	1	5		
African American	1	5		
Marital Status				
Married	11	55		
Divorced	1	5		
Separated	0	0		
Single	8	40		
Highest Education				
GED	1	5		
HS Diploma	3	15		
Some College	3	15		
Associate's Degree	3	15		
Bachelor's Degree	9	45		
Master's Degree	1	5		
Doctorate Degree	0	0		
Professional Degree (MD, JD)	0	0		
Total	20			

Research Question 1

Are there statistically significant differences in neurocognitive scores following 2 and/or 6 weeks of rTMS treatment as compared to pre-treatment? Prior to carrying out the research question 1 analyses, Pearson correlations were conducted to assess for appropriate covariates to be included in the repeated measures ANOVA (baseline, 2 weeks, post treatment). More specifically, correlations were conducted between all potential covariates and each cognitive domain (Executive Functioning, Complex Attention, Cognitive Flexibility) at each time point (pre-treatment, 2 weeks, post-treatment). Bi-serial correlations were conducted for all continuous variables (e.g., BDI-II and BAI score pre- to post-treatment change, number of sessions, age, baseline BDI-II and BAI scores), while categorical and ordinal variables (e.g., sex, education level, and marital status) were tested using Spearman's Rho analyses. Results, as seen on Table 2, did not identify any significant covariates for all three baseline neurocognitive domains (i.e., Executive Functioning, Complex Attention, Cognitive Flexibility).

This research question was examining whether a course of low-frequency, right-sided rTMS for the treatment of depression leads to changes in neurocognitive scores throughout treatment. CNS Vital Signs was used to assess cognition at pre-treatment, 2 weeks, and end of treatment. However, only data for the cognitive domains associated with functions implicated by the stimulation site (i.e., DLPFC): Executive Functioning, Complex Attention, and Cognitive Flexibility were used to address this research question. Three independent, repeated measures ANOVAs (baseline, 2 weeks, post treatment) were conducted to compare standard mean score differences for each cognitive domain

(Executive Functioning, Complex Attention, Cognitive Flexibility). All mean scores and standard deviations are reported in Table 3.

The one-way repeated measure ANOVA demonstrated significant improvements in executive function, $F(1,19) = 9.76$, $p = .000$, $\eta^2_p = 0.339$. Post-hoc Tukey's LSD analyses revealed that Executive Functioning mean scores at 2 weeks (102.95 ± 19.63) and post-treatment (108.75 ± 12.94) were both significantly greater than pre-treatment (88.25 ± 24.71) mean scores ($p < .05$). While there was a slight increase in mean score from 2 week to post-treatment, this increase however was not statistically significantly higher. Thus, in terms of Executive Functioning performance, significant improvements were found after 2 weeks, with those gains remaining stable at post-treatment (Figure 1).

Similarly, the second repeated measure ANOVA conducted comparing neurocognitive mean scores for Complex Attention, again showed significant improvements when all three time points were accounted for, $F(1,19) = 4.798$, $p = .014$, $\eta^2_p = 0.202$. Complex Attention mean scores at 2 weeks (90.25 ± 37.92) and post-treatment (99.15 ± 10.80) were both significantly greater than pre-treatment (76.55 ± 40.47) mean scores ($p < .05$). Also like Executive Functioning, while there was a slight increase in mean score from 2 week to post-treatment, this increase was not statistically significant (Figure 2).

The final repeated measure ANOVA showed Cognitive Flexibility, $F(1,19) = 10.18$, $p = .000$, $\eta^2_p = 0.361$, also differed significantly across the three time points. For Cognitive Flexibility, post-hoc Tukey's LSD tests revealed findings mirroring those of Executive Functioning and Complex attention with statistically significant increases from pre-treatment (84.50 ± 27.39) to 2 weeks (98.60 ± 21.41) and pre-treatment to post

treatment (106.50 ± 12.58), but no statistically significant increases between 2 week and post-treatment (Figure 3).

Table 2

Pearson Correlations between Potential Covariates and Neurocognitive Domain Scores (Executive Functioning, Complex Attention, Cognitive Flexibility) at 3 Time Points (Pre-Treatment, 2 Weeks, Post-Treatment)

Variables	Executive Functioning			Complex Attention			Cognitive Flexibility		
	Pre	2w	Post	Pre	2w	Post	Pre	2w	Post
BDI-II score change	-.30	-.30	-.09	-.16	-.29	-.08	-.28	-.39	-.12
BAI score change	.01	.20	.16	.18	.33	.17	.02	.18	.11
# of Sessions	-.17	-.12	-.31	-.20	-.08	-.25	-.19	-.14	-.30
Baseline BDI	-.41	-.23	-.44	-.50*	-.19	-.33	-.48*	-.31	-.47
Baseline BAI	-.20	-.06	-.30	-.28	.03	-.24	-.25	-.05	-.29
Age	-.11	-.01	-.37	-.24	-.20	.05	-.15	-.14	-.37
Sex	-.27	-.17	-.13	-.07	-.06	.15	-.25	-.09	-.16
Marital Status	.19	.16	-.01	.29	.34	.25	.23	.27	-.00
Education Level	.50*	-.01	.20	.42	-.03	.44	.51*	.08	.26

* = $p < .05$

Table 3

Means and Standard Deviations at Pre-Treatment, 2 weeks of treatment, and Post-Treatment for Executive Functioning, Complex Attention, and Cognitive Flexibility Neurocognitive Domains

	Pre-Treatment Mean (SD)	2 week (SD)	Post-Treatment Mean (SD)
Executive Functioning	88.25 (24.71)	102.95 (19.63)	108.75 (12.95)
Complex Attention	76.55 (40.47)	90.25 (37.92)	99.15 (10.80)
Cognitive Flexibility	84.47 (28.14)	99.32 (21.75)	106.37 (12.91)

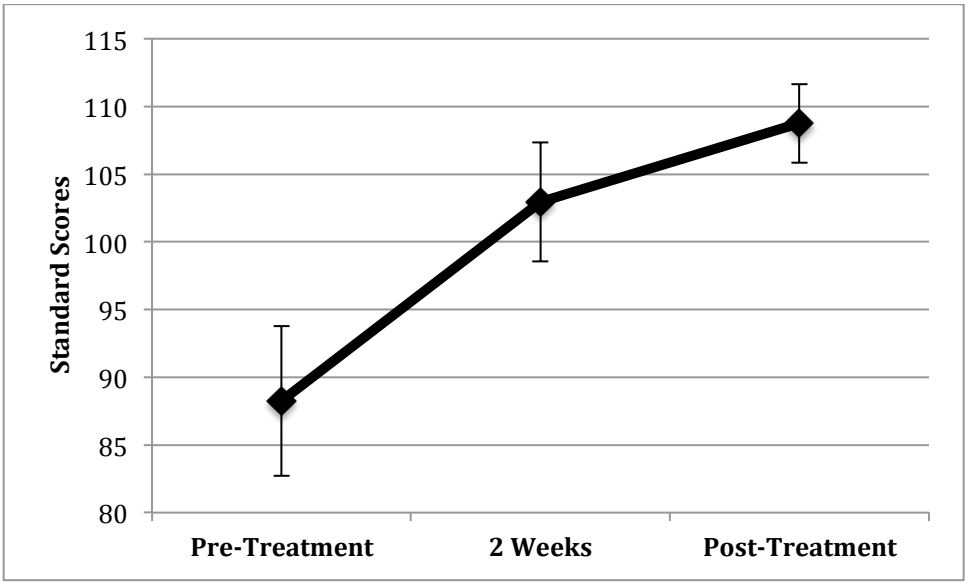

Figure 1. Executive Functioning 3-Time Point Standard Score Means

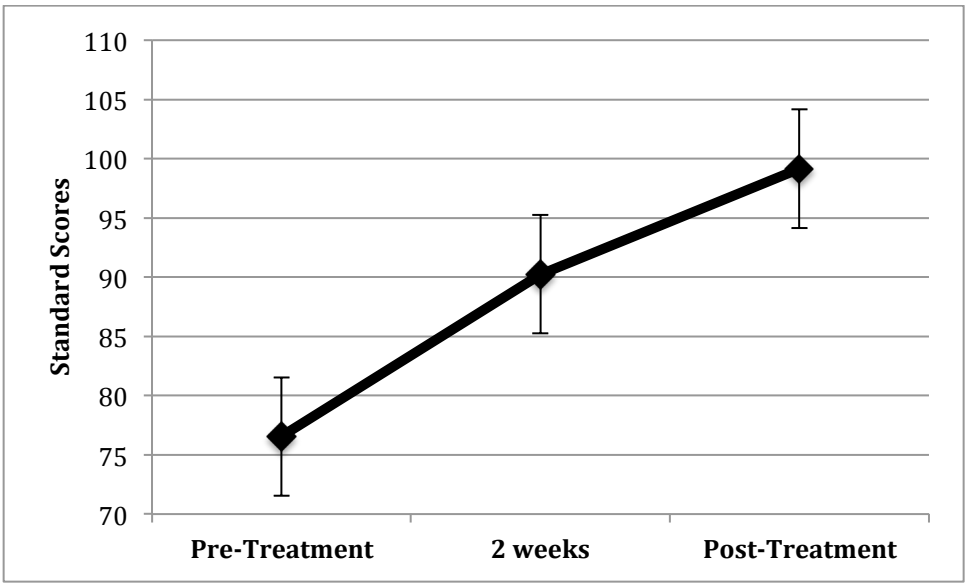

Figure 2. Complex Attention 3-Time Point Standard Score Means

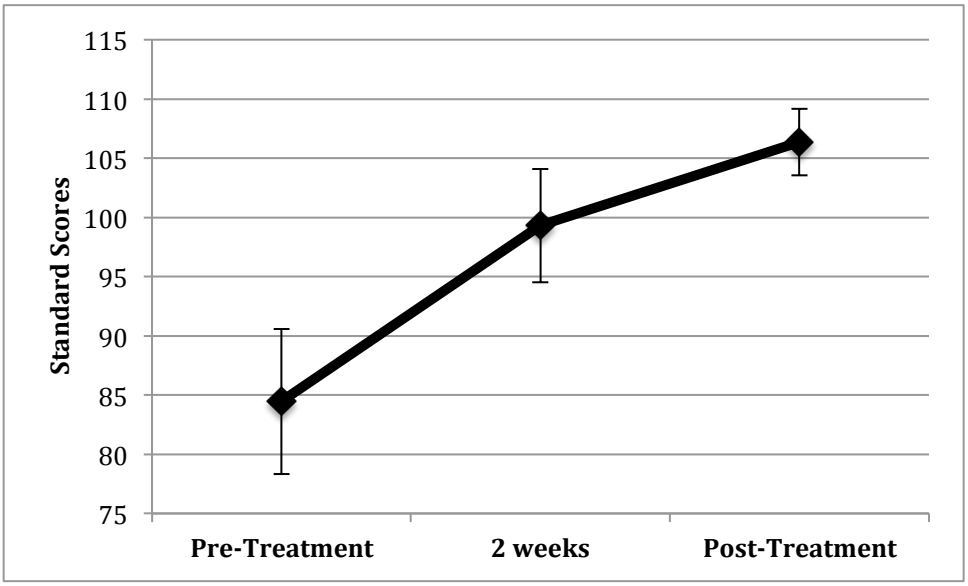

Figure 3. Cognitive Flexibility 3-Time Point Standard Score Means

Research Question 2

If significant improvements in neurocognitive scores are found, do these improvements occur independent of a reduction in depression and anxiety scores?

This research question examined whether neurocognitive improvements were more prominently associated with stimulation of neuronal activity to the DLPFC. Correlational analyses were conducted to examine the relationship between neurocognitive score change from pre-treatment to post-treatment and depression and anxiety score change from pre-treatment to post-treatment. Score change was calculated and represented as a percentage in which the difference between pre-treatment and post-treatment scores is divided by the pre-treatment score. Six Spearman's rho correlational analyses were conducted assessing the association between each neurocognitive domain (i.e., Executive Functioning, Complex Attention, and Cognitive Flexibility) and BDI-II percent change score and BAI percent change score. Results revealed that neither BDI-II nor BAI change scores were significantly correlated with Executive Functioning change scores, Complex Attention, or Cognitive Flexibility. Correlations are reported on Table 4.

Table 4.

Correlations between each Neurocognitive Domain Change Score and BDI-II and BAI Change Scores Pre- to Post-Treatment

	BDI-II (% Change)	BAI (% Change)
Executive Functioning (% Change)	.176	.055
Complex Attention (% Change)	.145	-.320
Cognitive Flexibility (% Change)	.152	.053

*p< .05

CHAPTER IV

DISCUSSION

TMS is emerging as a new and effective treatment alternative for the medication and psychotherapy resistant population, which continues to demand clarification regarding aspects of the treatment that can positively or negatively impact patient functioning. For that reason, exploring the issue of neurocognitive functioning in this patient population represents a significant contribution to the TMS and depression literature.

The aim of the present study was to examine whether an experimental, low-frequency dose of rTMS, which has been shown to contribute to treatment gains for treatment-resistant depression in previous research but is not yet FDA approved, leads to improvements in neurocognitive test scores from pre-treatment to post-treatment. This is an imperative question to address as current literature only provides evidence of neurocognitive change associated with a shorter course of treatment than has been found to be the most clinically efficacious for sustained mood improvement or with treatment limited to left sided treatment applications (George et al, 2010, O'Reardon et al., 2007, Wasserman, 1998, Little et al., 2000; Speer et al., 2001; Avery et al., 1999; Padberg et al., 1999; Triggs et al., 1999; Loo et al., 2001; Bayan, 2013). The study further aimed to characterize the trajectory of neurocognitive change that occurs throughout the course of treatment by examining neurocognitive score differences from pre-treatment to 2 weeks to post-treatment. Specifically, do improvements exist after 2 weeks of treatment, and, if so, do these improvements stabilize or further increase? Lastly, given that prior studies

have evidenced neurocognitive improvements independent of positive mood changes (Vanderhasselt et al., 2009, Rossi et al., 2009), the present study also examined whether the evidenced neurocognitive improvements were associated primarily with improvement of mood or stimulation of neuronal activity at the targeted treatment site (i.e., DLPFC).

Prior studies investigating neurocognitive effects associated with rTMS, have offered evidence that rTMS is not associated with adverse neurocognitive effects. Rather, previous studies have found improvement, or trends toward improvement, in the neurocognitive domains of memory, executive functioning, and motor speed (Little et al., 2000; Speer et al., 2001; Avery et al., 1999; Padberg et al., 1999; Triggs et al., 1999; Loo et al., 2001, Moser et al., 2002, Martis et al., 2003, Schulze-Rauschenbach et al., 2005). As previously mentioned, these studies utilized relatively shorter treatment session frequencies (e.g., 5 to 15 sessions) than were implemented in the current study (i.e., 35 sessions) or were limited to left-sided treatments. However, it is theorized that a longer treatment course is more likely to lead to greater, more sustainable effects in neurocognition as has been found for treatment of depression with TMS. Thus, the expected outcome was that rTMS would show a significant improvement in neurocognitive scores from pre-treatment to post-treatment.

As expected, results of rTMS neurocognitive score data revealed statistically significant improvements for all three neurocognitive domains (i.e., Executive Functioning, Complex Attention, and Cognitive Flexibility) across the three time points (i.e., pre-treatment, 2 weeks, and post-treatment). Regarding the differences between the three time points (i.e., pre-treatment, 2 weeks, and post-treatment) it was hypothesized that improvements in neurocognitive scores would be observed after 2 weeks of treatment

with continued improvements (or increases) in scores at post-treatment. However, results revealed statistically significant differences across test administrations only when all three test administrations were accounted for in the model. Post-hoc analyses demonstrated a pattern of statistically significant improvements in scores from pre-treatment to 2 weeks. No statistically or clinically significant improvement or increase was found from 2 week to post-treatment for Executive Functioning, Complex Attention, and Cognitive Flexibility although scores did increase from 2 weeks to 6 weeks. Therefore, in terms of change trajectory overall, based on the present results, it appears that the greatest neurocognitive improvement takes place during the first two weeks of treatment with a stabilizing (not declining) effect thereafter. Although the hypothesis that a longer treatment course of rTMS will lead to greater neurocognitive improvements was not supported, significant improvements in neurocognition were found nonetheless and were supported by medium effect sizes. The observation that cognitive enhancements associated with rTMS are predominantly accounted for in the first 2 weeks of treatment is consistent with previous findings. In their systematic review, Guse, Falkai, and Wobrock (2009) found that in the majority of studies subjects had 10 stimulation sessions in 2 weeks. The frequencies ranged from 10 Hz and 20 Hz, the motor threshold between 80 and 100%. In consideration of all positive cognitive outcomes, those studies using stimulation over a period of 2-4 weeks seem to be most effective. Two studies, which attained significant improving effects with 10-20 Hz, assessed five rTMS sessions only (Moser et al., 2002; Triggs et al., 1999). In two other studies, participants received one sham and one real rTMS session (Rektorova et al, 2005; Vanderhasselt et al., 2006). Five studies were lacking significant cognitive improvement, but indicated a trend of cognitive

amelioration (Boggin et al., 2005; Jorge et al., 2004; Loo et al., 2003; Mosimann et al., 2004; Rosa et al., 2006).

Given the evidence that neurocognitive changes appear to take place fairly quickly, further implies that neurocognitive change likely takes place independent of positive mood changes, or improvements in depression and anxiety scores, since abatement of this symptomology requires longer, more consistent stimulation of the DLPFC to maintain activity (in this sample 4-6 weeks). The finding that neurocognitive changes take place independent of mood changes was corroborated by Vanderhasselt et al. (2009), who in fact did find improved scores on a test of executive functioning after only one session of TMS in a depressed sample and no associated clinical improvement. The present study further validates this finding and supports the hypothesis that neuronal stimulation yields positive effects on neurocognition regardless of improvement in mood. Results of the current study revealed changes in depression and anxiety scores that were not significantly correlated with Executive Functioning, Complex Attention, and Cognitive Flexibility change scores. This finding demonstrates the functional impact of TMS' role in stimulating neuronal activity in focal regions of the brain implicated with particular cognitive functions and may suggest significant implications on the treatment of neurocognitive deficits as a result of other neuropsychiatric and neurological illness or injuries. Studies examining changes in cerebral functions following rTMS for a variety of diagnoses are available and though findings are inconsistent, many demonstrate selective cognitive improvement. When studying patients with schizophrenia Huber, Schneider, and Rollnik (2003) found improvements in psychomotor speed for women only when using high-frequency stimulation to the left DLPFC. In another study

involving patients with schizophrenia, however, Sachdev, Loo, Mitchell, and Malhi (2005) found no significant improvements. Martis, Alam, Dowd, et al., (2003) found improvements in working memory, executive function, objective memory, and fine motor speed for patients with bipolar when using 10Hz to the left DLPFC. Jorge, Robinson, Tateno, et al., (2004) observed a trend toward general cognitive improvement in patients with post-stroke depression when using 10 Hz to the left DLPFC. Boggio (2005) evidenced a trend toward improvement in executive function when using 15 Hz to the left DLPFC in patients with combined Parkinson's disease and depression. In patients with subjective memory complaints, Sole-Padulles, Bartres-Faz, Clemente, Mollineubevo, et al. (2006) demonstrated improvements in associative memory. Finally, in a study by Castel-Lacanal, Tarri, Loubinous, et al. (2014), found that following brain injury, rTMS restored the interhemispheric interactions following stroke. Additional results showed improvement in motor recovery, aphasia, and visuospatial neglect. Taken together, these studies are promising but again, because findings are inconsistent, and because the pathophysiological and neurobiological basis on these improvements is unclear, additional studies including genetics, experimental neurophysiology, and functional brain imaging are necessary to explore stimulation-related functional changes in the brain.

Limitations and Design Considerations

One major consideration and limitation of the current study is the small sample size. It was evident that this was a major factor in under-powering potentially significant results, particularly for post-hoc analyses. Patient recruitment and participation is often limited and difficult to ascertain due to the continued lack of awareness of this treatment option in addition to the high cost of the treatment and tentative insurance coverage.

Even so, obtaining a larger sample size would enable not only the potential for greater power and larger effect sizes, but it would also allow for a more representative sample of depressed patients particularly with regard to baseline cognitive functioning. Sample bias is likely to be an issue when sample size is severely limited, in combination with having a treatment that is not as accessible to the general public. Given the high cost of this treatment, the sample is liable to consist of individuals of higher socioeconomic status (SES). Thus, a larger and more representative sample would allow for greater statistical power and greater generalizability.

Another significant limitation relates to the lack of a depressed control group, receiving standard treatment and not rTMS treatment, and completing the neurocognitive battery at two different time points. This would allow controlling for possible placebo effects associated with receiving rTMS versus no treatment or standard treatment. However, the most beneficial and efficacious design would be the randomized-controlled trial in which depressed patients are randomized to either a rTMS treatment condition or a rTMS sham control condition. rTMS sham is a control device specially constructed for research purposes, more specifically randomized-controlled trials. It mimics the sound and sensation associated with rTMS treatment, without the neuronal stimulation. Thus, both groups go through an identical procedure, which allows for a more powerful method of controlling for placebo effects.

Participant selection procedures are typically meant to identify a subset of depressed patients (i.e., treatment-resistant subset) that allows for greater homogeneity in the sample. However, achieving homogeneity will always pose a major challenge given that heterogeneity is rather inherent in the symptom and disease phenotype of depression.

In this particular study, the sample was primarily comprised of Caucasian women with at least a high school education. This of course limits the generalizability of findings. , Heterogeneity, as it pertains to depression severity, symptom rate of recovery, treatment adherence, and concomitant medication treatment and/or psychotherapy, also poses potential confounds that could significantly impact response to rTMS from a neurocognitive standpoint. This could also be greatly controlled for via a randomized-control study design. In a randomized-controlled study, the act of randomly assigning subjects to either the intervention (receiving TMS treatment) or control (receiving sham TMS) group ensures that, on average, no systematic differences (i.e., factors listed above) exists between groups and thus outcomes can be seen as attributable solely to the intervention.

Another potential limitation is the battery utilized to assess the specific functions implicated with the DLPFC. While CNS Vital Signs has shown promising reliability and validity properties, particularly in its utility for research in a clinical setting (Gualtieri & Johnson, 2006), it is possible that more extensive testing of the targeted domains (e.g. attention and executive functioning) would provide a more accurate representation of each group's neurocognitive profile.

Similar to many other rTMS studies, this study was limited by the lack of follow-up measures. It is therefore unknown how long the observed effects of rTMS on cognitive function will persist. However, while the duration of the induced cognitive effects are lacking, one can assume, based on remaining effects of psychopathology from other studies (e.g. improvement of mood), cognitive improvement will persist for a period of time.

A final limitation concerns the positioning of the coil. This study used the Pascual-Leone method whereby the coil was placed 5 cm rostrally from the hot spot of the primary motor cortex to identify the DLPFC and 2 cm rostrally to identify the SMA. Neuronavigation studies have shown that individual fMRI-guided TMS neuronavigation yielded the strongest behavioral effect size as compared to an EEG-system approach and the Pascual-Leone method (Sack et al., 2009). It may therefore stand to reason that cognitive changes may be impacted by correct coil positioning.

The aforementioned limitations demand a careful analysis of the findings and interpretations. First, while no significant changes in cognitive functioning were evidenced from 2 weeks to post-treatment, it may be possible that in fact, longer treatment does result in greater change, but can only be evidenced by a larger sample size or by more precise coil positioning. At the same time, it is also possible that cognitive improvements may be more likely in certain treatment-resistant patient cohorts like those represented in this sample and thus, generalizing these findings should be done cautiously. The direct influence of rTMS on cognitive enhancement also should be considered thoughtfully due to the number of potential confounds and the possibility of placebo effects. It may also be that because of the close connection and intra-dependability of the cognitive abilities associated with the frontal cortex, along with the psychometric limitations of the tests used to measure them, results only point to general cognitive domain improvements and do not specifically delineate between them. Finally, while the cognitive improvements shown in this study are exciting, their durability is not known.

Conclusions

The present study was able to contribute to the current empirical knowledge maintaining rTMS' safe and beneficial use for treatment-resistant depression (TRD). More specifically, it substantiates the use of right-sided, low-frequency rTMS as a treatment alternative to ECT as it preserves cognitive functions. It extends the existing evidence for the ongoing case in making rTMS a first line of treatment for TRD with further elucidation of additional rTMS treatment parameter options. This study also provided support for improved functions associated with frontal-lobe functioning: executive functioning, attention, and cognitive flexibility. This is of paramount significance as these are functions necessary for optimal functioning and overall well-being.

The results of this study also helped to facilitate the understanding of how functional processes are actuated by these neurophysiological and neuroplastic changes in the brain. Previous brain imaging studies have demonstrated metabolic and cerebral blood flow alterations in the DLPFC, as well as in other limbic, paralimbic, frontal and prefrontal regions, after application of rTMS (Kito, Fujita & Koga, 2008, Spear et al., 2000, Kito et al., 2009). Furthermore, there has been evidence of grey matter density alterations in direct and remote areas of the site of rTMS stimulation after as little as five days of treatment, as well as direct evidence of rTMS-induced long-term potentiation in humans after a single train of repetitive stimulation (May et al, 2006; Esser et al, 2006). This study adds to this by demonstrating a clear pattern of neurocognitive improvements that tend to take place sometime during the initial 2 weeks of treatment. In addition to elucidating this neurocognitive change pattern, the current study also corroborated the

finding that improvements are associated with low frequency rTMS and that they occur independent of mood changes, thus likely a direct effect of neuronal stimulation. This is an important contribution to the rTMS literature as it allows for broader treatment implications for neurocognitive impairment caused by other injuries or pathologies, such as the effects of stroke, TBI, or Parkinson's. This opens up the possibility for research to investigate the utility of TMS in stimulating underactive or damaged regions of the brain identified by MRI, for example, which is also having significant cognitive or functional effects on the patient and warranting some form of intervention. Because the TMS effects on cognition are also relatively quick (2 weeks), it also serves as a treatment option that is not time consuming or as costly as current rTMS treatment courses for neuropsychiatric disorders. However, with that said, further investigation into the durability of cognitive effects, the influence of potential confounds and placebo effects, and the generalizability of these findings is still necessary. This would be ideally accomplished with a randomized clinical trail, which includes a sham condition. Demonstrating TMS' capacity for neurocognitive improvement is believed to be a substantial finding that can greatly facilitate a much larger and broader role for TMS in the field of neuropsychiatry. However, the provision of evidence of sustainable gains in cognition will prove to be prolific beyond the field of neuropsychiatry.

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EDUCATION

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2005 – 2007 **College of William and Mary**
Williamsburg, Virginia
M.Ed., Community and Addictions Counseling, *magna cum laude*

1997 – 2001 **James Madison University**
Harrisonburg, Virginia
B.S., Psychology, minor in Substance Abuse Intervention

PRE-DOCTORAL CLINICAL PSYCHOLOGY INTERNSHIP:

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Physical Med. & Rehabilitation (Major Rotation), *Sentara Norfolk General Hospital*
Adult and Pediatric Neuropsychology (Minor Rotation), *EVMS Neuropsychology*
Organ Transplant Evaluation (Adjunct Clinical Experience), *Sentara Heart Hospital*
Outpatient Clinic (Minor Rotation), *EVMS Dept. of Psychiatry and Behavioral Sciences*.
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PRESENTATIONS

Chappell, A., Neumann, S.A., Sayegh, P.A., Seagly, K., Bayan, S. (2014, November). *Neurocognitive Performance as a Function of Right-Sided, Low-Frequency rTMS Administration in Treatment Resistant Depression.* Poster presented at the National Academy of Neuropsychology Annual Convention, Fajardo, Puerto Rico.

Chappell, A., Estes, B., Winstead, B. (2013, October). *Levels of Functional Independence and Performance on Embedded Measures of Effort*. Poster presented at the National Academy of Neuropsychology Annual Convention, San Diego, California.

Chappell, A. (2014, October). *Levels of Functional Independence and Performance on Embedded Measures of Effort*. Presented at the Virginia Consortium Program in Clinical Psychology Annual Research Day.

Banks, G., **Chappell, A.** (2006, May). *Comprehensive, Community-Wide Substance Abuse Needs Assessment.* Presented at the Historic Triangle Substance Abuse Coalition Annual Convention, Williamsburg, Virginia.