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Testing the Efficacy of Transcranial Magnetic Stimulation (TMS) in Treating Depression in Patients with Cognitive Impairment

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TESTING THE EFFICACY OF TRANSCRANIAL MAGNETIC STIMULATION (TMS) IN TREATING DEPRESSION IN PATIENTS WITH COGNITIVE IMPAIRMENT

by

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ABSTRACT

TESTING THE EFFICACY OF TRANSCRANIAL
MAGNETIC STIMULATION (TMS) IN TREATING
DEPRESSION IN PATIENTS WITH COGNITIVE IMPAIRMENT

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The purpose of this study is to (1) examine the efficacy of Transcranial Magnetic Stimulation (TMS) in treating depression among individuals with cognitive impairment and (2) to examine if TMS is capable of facilitating cognitive improvements independent of mood improvements. Mild cognitive impairment (MCI) is often seen as a pre-clinical stage to dementia, and depressive disorders are highly prevalent among both MCI and dementia. There is a large body of research that has linked depressive disorders as a prodromal symptom of MCI and the later development of dementia. While some researchers debate whether or not this link between depression and MCI/dementia is a true prodromal relationship, or if depression is independently comorbid with MCI/dementia, it remains clear that these disorders occur together in high prevalence rates.

The goal of this study was to determine whether or not Transcranial Magnetic Stimulation (TMS) might demonstrate treatment efficacy in treating depressive symptoms among individuals who meet MCI criteria. TMS has been previously approved by the FDA to treat major depressive disorder (MDD); however, very few research studies have been performed to analyze TMS' ability in treating MDD among individuals with MCI.

By analyzing treatment data from individuals who do and do not meet MCI criteria, TMS does appear to demonstrate positive treatment efficacy for treating depressive symptoms among

individuals who meet MCI criteria. TMS also appears to be equally efficacious in treating depressive symptoms among this group in comparison to individuals without MCI. TMS also produces positive changes in neurocognitive functioning, both in the MCI and non-MCI groups; however, the results show that these changes in neurocognitive functioning likely occur as a function of depressive symptom reduction.

This thesis is dedicated to my beautiful wife,
who supported me unconditionally through this entire process.

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INTRODUCTION

Literature Review

Depression is a common phenomenon among individuals with mild cognitive impairment (MCI) and dementia. According to many researchers, MCI is often a precursor to dementia, and MCI is often referred to as pre-dementia, pre-clinical phase, or transitional stage to developing a dementia diagnosis (Albert, et al., 2010; Alzheimer's Association, 2016; Gualtieri & Johnson, 2005; Kelley & Peterson, 2007; Nardone, et al., 2014; National Institute on Aging, 2015; Peterson, 2007; Peterson, 2013). Specific conversion rates from MCI to dementia diagnoses seem to vary among the research. The average conversion rate is approximately 10-15% (Mitchell & Shiri-Feshki, 2009); however, the conversion rate has been measured up to 40% (Farias, Mungas, Reed, Harvey, & DeCarli, 2009; Mitchell & Shiri-Freskhi, 2009).

Current methods for treating depression in individuals with MCI and dementia, namely antidepressant medications (e.g., SSRIs) and electroconvulsive therapy (ECT), have been scrutinized within the body of research due to concerns about their efficacy and safety among this population. The purpose of this research study is to examine the effects of transcranial magnetic stimulation (TMS) on treating depression and improving cognitive functioning among individuals with MCI.

There is markedly little research on MCI, as it is often difficult to detect in its beginning stages, and it often goes undiagnosed until it develops into dementia (Saykin & Rabain, 2014). According to the Alzheimer's Association (2016), approximately 60-80% of all dementia diagnoses are Alzheimer's disease (AD; p. 6). Because of the disproportionate amount of AD in comparison to the many other forms of dementia, a large bulk of the research body focuses on AD, leaving other forms of dementia underrepresented in the literature.

Dementia, also known as Major Neurocognitive Disorder (MND), is a growing phenomenon around the world. According to the World Health Organization (2015), the number of people living with dementia diagnoses in 2015 was approximately 47.47 million people. This number was projected to increase to 76.36 million people worldwide in 2030 (60.86% increase) and up to 135.46 million people worldwide in 2050 (77.40% increase from 2030; 185.36% increase from 2015). This increase in prevalence rates is likely due to the growing population and increasing life expectancy of the general population (Alexopolous & Kelly, 2009; Alzheimer's Association, 2016; Kelly & Peterson, 2007; National Institute on Aging, 2015; Rabey & Dobrenevsky, 2016; Saykin & Rabin, 2014). While the precise numerical increase tends to vary across sources, it is clear that the increase in MCI/dementia is a serious issue around the world.

Common comorbid psychological diagnoses with dementia are depressive disorders. The Alzheimer's Association (2016) has identified depression as a possible early symptom in developing MCI/dementia. While there is some debate in the literature as to whether depression is a result of neurophysiological changes in the brain caused by dementia, or if depression could be an early symptom or risk factor of developing MCI/dementia, research is providing increasing support for depression as prodromal to MCI and dementia.

Depression in the elderly population may first appear as symptoms of cognitive decline, especially in the following areas of cognition: information processing speed, episodic memory, and executive function (Story, Potter, Attix, Welsh-Bohmer, & Steffens, 2008). Story, et al. (2008) found that individuals with Major Depressive Disorder displayed performance levels on neurocognitive measures similar to those who demonstrate true cognitive decline. However, after treating for depression, cognitive scores increased in a progression towards average functioning

(Story, et al., 2008), thus highlighting the possibility that depressive disorders are linked with outward declines in cognitive functioning.

According to an extensive narrative review by Byers and Yaffe (2011), "depression can impair cognitive functioning leading to 'pseudodementia'" (p. 2). By calling the outward cognitive deficits brought about by depression "pseudodementia," the line between the two disorders (i.e. dementia and depression) is blurred. When these two disorders occur together, it can become difficult for clinicians to determine their exact relationship (Byers & Yaffe, 2011). This information is also supported by Peterson (2007), and Saykin and Rabin (2014), who stated, "…depression alone can cause significant cognitive impairment" (p. 249). The term "pseudodementia," or "depressive pseudodementia," has appeared across the body of research as a means to describe this relationship between depressive disorders and cognitive symptomology (Bieniek, et al., 2014; Byers & Yaffe, 2011; Hancock & Larner, 2014; Heser, et al., 2016; Paula, et al., 2013).

There is increasing evidence supporting depression as a prodrome to dementia. In other words, depression occurring later in life could potentially be viewed as a harbinger of developing MCI and subsequent dementia (Hesser, et al., 2016; Saykin & Rabin, 2014; Segal, Coolidge, Cahill, & O'Riley, 2008). A research study that sought to examine this potential prodromal link between depression and dementia was that of Han, et al. (2008). The findings of this study showed that at 12-month follow up appointments, over half of the initial patients (n = 281, age 65 and older) who were diagnosed with major or minor depression, as defined by the *DSM-IV*, scored significantly lower on the Mini-Mental State Examination (MMSE) than upon intake. This decline in cognitive status remained significant after successfully treating the depressive disorder (Han, et al., 2008), indicating that the cognitive deficits present among the participants

was not caused by a "depressive pseudodementia." As a result, this study does provide support that depression may be viewed a potential prodromal factor to cognitive decline.

Thomas and Bennett (2014) examined correlations between early-life depression and later-life onset of dementia. Their narrative review provided evidence for two hypotheses: (1) early-life depression can act as a potential risk factor for later-life dementia, and (2) later-life depression can be viewed as a prodrome to the onset of dementia. According to their review, both depression and dementia were associated with white matter alterations in the brain, indicating either (1) shared risk factors, or (2) shared pattern of neurological damage (Thomas & Bennett, 2014). Once again, the research provides increasing support for the notion that depression and dementia are linked in a prodromal relationship, meaning depression is a possible risk factor or indicator for the onset of MCI/dementia and related cognitive declines.

Mirza, et al. (2016) conducted a longitudinal study embedded within a much larger study (the Rotterdam Study), ongoing since 1990, during which participating individuals were monitored for any major events. Among the cohort selected for this longitudinal study (n = 3,325), the researchers found a significant relationship between high depressive symptoms later in life and the later onset of cognitive decline, MCI, and AD after the following potential confounds were controlled: age, sex, presence of the *APOEε4* allele, education level, body-mass index (BMI), smoking habits, alcohol consumption, general cognition (MMSE score), use of antidepressants, prevalent hypertension, Type 2 Diabetes or the use of any anti-diabetic medications, and previous myocardial infarction and stroke activity (Mirza, et al., 2016). These results provide further evidence for depression acting as a prodromal factor for cognitive decline, MCI, and dementia.

Castilla-Puentes and Habeych (2010) researched specific links between certain types of depressive disorders and dementia diagnoses. They analyzed the prevalence of different subtypes of depressive disorders in patients with AD (*n* = 2,947), vascular dementia (VaD; *n* = 725), and unspecified dementia (UD; *n* = 2,768). The subtypes of depressive disorders that were studied, based on the ICD-9 diagnostic codes, were major depressive disorder, depressive disorder not otherwise specified, dysthymic disorder, depressive psychosis, and adjustment disorder with depressive symptoms. They found that the overall prevalence rate of depressive disorders among individuals with dementia (*n* = 6,440) was 27.41%. Specifically, the prevalence rates were 44.14% in VaD; 32.48% in UD; and 18.53% in AD. VaD was found to have the highest rate of comorbid diagnoses of depressive disorders, including depressive disorder not otherwise specified, major depressive disorder, and dysthymic disorder. Adjustment disorder with depressive symptoms was most common among the UD group, and depressive psychosis was similar among all dementia groups (Castilla-Puentes & Habeych, 2010). Once again, it is evident that depressive disorders and dementia are highly linked in some way. Based on this evidence, it appears that VaD has the highest prevalence rates of depressive comorbidity among the other forms of dementia, with AD and UD showing significant comorbidity as well.

Byers and Yaffe (2011) provided further explanations for this apparent link between depression and dementia with their extensive narrative review. They discovered that approximately 20% of patients with AD, and 50% of patients with VaD, had a comorbid diagnosis of major depressive disorder (MDD). In order to explain this link, they developed four equally-plausible hypotheses based on their review of the literature: "(1) depressive symptoms often occur among patients with dementia; (2) depression may be a psychological reaction to early cognitive deficits; (3) depression can impair cognitive functioning leading to a

'pseudodementia' presentation; and (4) depression may be a risk factor or early symptom of dementia" (Byers & Yaffe, 2011, p. 2), particularly for VaD. However, Byers and Yaffe (2011) also state that the exact relationship between late-life depression and MCI/dementia is "unclear" (p. 8).

While the current body of literature is mixed, and no empirical consensus has been reached as to the exact nature of late-life depression and MCI/dementia, there does appear to be enough empirical support for the claim that late-life depression is prodromal to the development of MCI/dementia. As such, early intervention and treatment for late-life depression may act in a protective manner against the further development of MCI/dementia. While depressive symptoms may present in a depressive pseudodementia manifestation, empirical evidence has suggested that, if depressive symptoms are left untreated, further cognitive decline is highly likely, thus resulting in a more severe MCI/dementia diagnosis. However, if accurate diagnoses are made early and interventions are implemented, the continual neurodegeneration of "depressive pseudodementia" into true MCI/dementia may be prevented.

The most widely used method of treating depression among individuals with dementia diagnoses is the use of antidepressant medications, specifically selective serotonin reuptake inhibitors (SSRIs). There is some research that claimed SSRIs become less effective in older populations, such as the geriatric dementia population (Kitching, 2015, p. 209; McDonald, 2016, p. 1130). Supporting this claim, Farina, Morrell, and Banarjee (2016) conducted a literature review to examine the efficacy of antidepressant medications, specifically SSRIs, in the depressed dementia population. After reviewing 36 randomized controlled studies (n = 3,386), they found that the most significant effect of SSRIs was for mitigating agitation in the depressed dementia population, a claim which is also supported by the National Institute of Aging (2015, p.

37); however, their findings reflected a lack of efficacy for SSRIs in treating depressive disorders among individuals with dementia (Farina, et al., 2016). It is important to note that the research included in the narrative review was predominantly concerned with AD, with few included studies analyzing the effects of SSRIs among individuals with VaD, fronto-temporal dementia (FTD), or dementia not specified. Specific analyses of the effects of SSRIs among these subtypes of dementia are not provided (Farina, et al., 2016).

Enache, Winblad, and Aarsland (2011) provided further support for the lack of treatment efficacy of antidepressants for depression among dementia populations. In their narrative review, they found eleven studies (n = 1,514) that examined the effects of antidepressant medications on treating depression among individuals with dementia. Results were largely inconsistent with each other. Byers and Yaffe (2011) also stated that the research body at the time demonstrated a lack of treatment differences between placebo and treatment groups. Due to these inconsistencies, the efficacy of antidepressants for individuals with MCI/dementia was called into question (Byers & Yaffe, 2011; Enache, et al., 2011).

Other treatment methods for depression in individuals with dementia include some cognitive psychosocial strategies such as reminiscence therapy, music, cognitive stimulation, conversation, and physical activity when it can be applied (Enache, et al., 2011; Moyle, Hsu, Lieff, & Vernooij-Dassen, 2010). However, there is little research to support the efficacy of these cognitive and psychosocial strategies. Due to cognitive impairment, many forms of cognition-based therapies, including Cognitive Behavioral Therapy (CBT), are likely to be less effective for patients with cognitive impairment and dementia (Enache, et al., 2011).

In a narrative review by Kolshus, Jelovac, and McLaughlin (2016), two types of brief-pulse ECT were found to be the most commonly used when treating depression among

individuals with dementia: bitemporal electrode placement and right unilateral ECT. Of these two methodologies, bitemporal electrode placement was found to be the most commonly used. Seven ECT studies (n = 792) were included in the review, analyzing both forms of ECT treatment methods. Both bilateral electrode placement and unilateral ECT have been shown to decrease depressive symptomatology in degrees that are both clinically and statistically significant; however, high-dose unilateral ECT treatments have shown fewer cognitive side-effects than moderate-dose bitemporal treatments (Kolshus, et al., 2016).

ECT as a general form of treatment does cause certain cognitive side effects after treatment, some remaining for a short duration after the treatment, and others lasting slightly longer. Immediate disorientation is the most frequent side-effect, and it usually dissipates within the first hour after treatment (Kolshus, et al., 2016). Many other cognitive side effects tend to last for approximately two to three weeks after treatment. Bilateral ECT has been shown to create "more global cognition deficits, delayed verbal memory, and autobiographical memory impairments in comparison to unilateral ECT" (Kolshus, et al., 2016, p. 519). Unilateral ECT treatment has also been associated with "decreases in verbal learning, delayed verbal memory, visual recognition impairments, and semantic memory retrieval deficits" (Kolshus, et al., 2016, p. 519). While research has shown that bilateral ECT methodologies produce more cognitive side-effects than unilateral ECT methodologies, the fact remains that both methodologies create cognitive side-effects that can last for weeks, or longer, after treatment sessions. Moreover, elderly patients with cognitive deficits without dementia diagnoses, such as those with MCI or cognitive deficits as a result of depressive disorders (Byers & Yaffe, 2011; Saykin & Rabin, 2014; Story, et al., 2008), are more susceptible to these cognitive side-effects (Dybedal, Tanum, Sundet, & Bjølseth, 2015).

Vagal Nerve Stimulation (VNS) is another FDA approved treatment for long-term, treatment-resistant depression for individuals age 18 and older. According to McDonald (2016), "there are no published studies currently addressing VNS [specifically] in the elderly" (p. 1133); however, analysis of patients age 65 and older receiving VNS in a larger registry sample showed promising results for its efficacy in improving depressive symptoms among the aforementioned individuals. It is important to note, though, that individuals age 65 and older comprised only 20 of the total 500 patients in the overall registry study (McDonald, 2016), thus providing too little information to come to concrete conclusions about VNS in the geriatric population. VNS also requires invasive surgery, during which surgeons must attach an electrode onto the left vagus nerve. This electrode is also connected to a stimulator implanted in the individual's chest wall. The devise releases electrical impulses that are sent via the stimulator in order to create therapeutic effects (McDonald, 2016, p. 1133). Because this is such an invasive procedure, it may not be a proper choice for elderly individuals with MCI or dementia diagnoses.

Based on the current treatment information found within the body of literature, it is clear that individuals with MCI/dementia and comorbid depressive disorders are in need of an alternative form of treatment. The goal of this research project was to determine if Transcranial Magnetic Stimulation (TMS) may be an efficacious form of treatment for this population. TMS has already been deemed an efficacious treatment method for individuals with depression (Lannone, Cruz, Brazil-Neto, & Boechat-Barros, 2016; Magnezi, Aminov, Shmuel, Dreifuss, & Dannon, 2016; McDonald, 2016; Perera, et al., 2016; Wani, Trevino, Marnell, & Husain, 2013), and it has been approved by the FDA as a treatment method for treatment-resistant depression (U.S. DHHS, FDA, & CDRH, 2011). TMS has also been found to be more cost effective and

patient-preferred over ECT (Magnezi, et al., 2016) and other conventional forms of treatment (Simpson, Welch, Kozel, Demitrack, & Nahas, 2009).

Brain stimulation as a therapeutic clinical technique began in the early 20th century, particularly with the development of ECT in 1937 (Horvath, Perez, Farrow, Fregni, & Pascual-Leone, 2011). Faraday's discovery (as cited in Horvath, et al., 2011) of electromagnetic induction ultimately marked the beginning of magnetic pulse stimulation as a therapeutic approach. The use of magnetic pulse stimulation was not developed until 1910, and it did not see human nervous system application until 1965 (Horvath, et al., 2011). After the first official TMS device was created in 1985, the applications of magnetic stimulation have expanded to what they are today, including the FDA approved treatment of depressive disorders (Horvath, et al., 2011; U.S. DHHS., et al., 2011).

TMS is a neuro-stimulation technique in which parts of the neocortex, approximately 2-3 cm deep, and underlying areas of the brain through transynaptic neuro-pathways can be innervated by brief, noninvasive magnetic currents. The electrical currents in the brain are enervated by brief magnetic fields discharged by a coil placed against the scalp, targeting a specific area of the brain (Cowey, 2005). Unlike other forms of neuro-stimulation, such as ECT, TMS does not directly produce electrical currents to stimulate the brain. Instead, TMS promotes neural activity via magnetic fields. ECT also typically requires anesthesia to facilitate muscle relaxation during the procedure (American Psychiatric Association, 1978), whereas TMS can be applied to patients while awake and alert without anesthesia. Due to the non-invasive nature of TMS, and its ability to increase neuroplasticity (Pascual-Leone, et al., 1999) and innervate areas of the brain associated with depressive symptoms (Arns, Drinkenburg, Fitzgerald, & Kenemans,

2012), TMS has been approved by the FDA as a treatment for treatment-resistant depression (U.S. DHHS, et al., 2011).

The success rates of TMS in its ability to treat treatment-resistant depression vary throughout the literature, mainly due to many studies using relatively small sample sizes. However, some meta-analyses have found TMS to be up to 80% effective in treating treatment-resistant depression (treatment success defined as the absence of depressive symptom relapse; Janicak & Dokucu, 2015), indicating that it is likely able to reduce depressive symptoms with little risk of relapse among 80% of the treatment-resistant population. Research has also shown TMS to produce long-lasting treatment effects after cessation of treatment (Machado, et al., 2013; Simpson, et al., 2009). In fact, some research indicates that TMS may have long-lasting benefits for up to 84.2% of patients who see clinical improvement of their depressive symptoms, with effects maintained at 6-month follow-up (treatment benefits defined by the absence of depressive symptom relapse; Janicak, et al., 2010). However, these success rates are found within younger to average age adult samples. Not enough data pertaining specifically to geriatric samples are available for success rates to be formulated for this group.

TMS as a treatment method for elderly and geriatric populations has been questioned by research, primarily due to "lack of evidence [for this age group]," lack of age-cohort inclusion, and "a lack of safety information" (Sabesan, et al., 2015, p. 170-171); however, Sabesan, et al. (2015) found evidence to support the use of TMS in the elderly/geriatric population. In their narrative review, they cited several studies in which there was no participant attrition due to adverse side-effects or safety complications. One study cited by Sabesan, et al. (2015), conducted by Jorge, Moser, Acion, and Robinson (2008), included two separate experiments (total n = 92, mean age = 63.85, age range unavailable). Both experiments addressed the safety

and efficacy of TMS in the elderly/geriatric population. According to Jorge, et al. (2008), the active treatment and sham treatment groups did not differ significantly in frequency of adverse side effects, and the active treatment group also showed significant improvements in symptomology, thus providing support for the safety and efficacy of TMS for this population.

There has been some concern within the literature as to whether or not TMS could be a viable treatment method for depression among individuals with MCI/dementia diagnoses. Cortical atrophy is often prevalent among individuals with MCI, and it is a key characteristic among many forms of dementia. As a result, it may be more difficult for TMS methodologies to effectively stimulate the targeted areas. In vascular dementia particularly, certain neuroanatomical circuits are disrupted, potentially making TMS less effective in neural activation (McDonald, 2016). However, there is evidence within the body of research that supports the claim that TMS can be used to increase cortical and neural excitability and neural plasticity among individuals with dementia diagnoses (Alberici, et al., 2008; Elder & Taylor, 2014; Issac, Chandra, & Nagaruju, 2013; Luber & Lisanby, 2014; Nardone, et al., 2015; Pennisi, et al., 2006), thus providing a counter-argument to many criticisms of the efficacy of TMS for this population.

Because TMS can stimulate and increase cortical and neural excitability and neural plasticity, it may be possible for TMS to improve cognitive performance among individuals with MCI and varying levels of dementia. While a vast majority of the research in this particular area has focused solely on AD, many studies have cited direct cognitive improvements among individuals ages 55-85 as a result of TMS treatment programs (Bentwich, et al., 2011; Cotelli, et al., 2006; Lee, Choi, Oh, Sohn, & Lee, 2016; Nardone, et al., 2014; Rabey & Dobrenevsky, 2016). However, it should also be noted that many of these studies also incorporated a form of

cognitive training to be performed either during or alongside the TMS treatment regimen (deemed TMS-Cog; Bentwich, et al., 2011; Lee, et al., 2016; Rabey & Dobrenevsky, 2016). Because of the combination of these two methodologies, it is unclear whether or not TMS alone may have a significant influence on cognitive performance.

One particular study conducted by Chappell (2016) found that TMS provides an efficacious treatment method for improving cognitive functioning. The sample from this study (n = 20) had a mean age of 42.35 (SD = 12.50), was predominantly female (75%), and was predominantly Caucasian (90%). Specifically, Chappell (2016) examined three cognitive domains in individuals with *DSM-IV* diagnoses of Major Depressive Disorder: executive functioning, complex attention, and cognitive flexibility. All three of these cognitive areas significantly improved after the first two weeks of treatment and stabilized after the second week. No significant improvements in cognition were noted after the second week of treatment (Chappell, 2016).

Statement of Purpose

For the purpose of this research study, there are two primary research questions of interest: (1) can Transcranial Magnetic Stimulation (TMS) be used effectively to treat depression in patients diagnosed with mild cognitive impairment (MCI), and (2) can TMS be used to improve cognitive functioning among the aforementioned individuals independent of mood improvements? We hypothesize that TMS treatment will improve depression levels as well as cognitive impairment, and the improvement in cognitive impairment will be independent of changes in depression levels. We also hypothesize that any treatment differences among depressive symptoms between individuals with MCI and individuals without MCI will not be statistically different – TMS will be equally efficacious in treating depressive symptoms for both

groups. The efficacy in treating depressive symptoms among non-cognitively impaired individuals has been well established in the literature; it is a goal of this study to determine if these treatment outcomes (i.e. clinically/statistically improved depressive symptoms) also extend to individuals with MCI.

Methodology

Sample

Data were derived from a larger study at Eastern Virginia Medical School (EVMS). The study protocol was approved by the Institutional Review Board of EVMS (IRB#: 10-07-FB-0135-EVMS). The purpose of this larger study is to establish a registry of data regarding information employed in clinical practice with patients receiving TMS for treatment of various psychological disorders (e.g. MDD, OCD, PTSD). At the time of this present study, the database contained 95 participants who have sought psychological treatment via TMS treatment regimens at EVMS. All participants in the database have volunteered and consented to have their treatment data archived (IRB#: 10-07-FB-0135; see Appendix A for registry consent form).

The database contained a total of 95 participants; however, after data cleaning procedures (see section, Data Reduction and Data Cleaning), only 68 participants were used in this study (N = 68).

A-Priori Power Analysis

A power analysis was conducted via G*Power utilizing effect size information found in the literature to determine the minimum sample-size requirement for this research study. According to the research regarding TMS treating depressive disorders, Cohen's d effect sizes range from small to medium (d = 0.35 to d = 0.76; Sabesan, et al., 2015). There is a lack of

information in the research body regarding the efficacy of TMS in treating cognitive impairments:

> …there are very limited available data in the use of these approaches [TMS] in the symptomatic [cognitive] treatment of dementias, the majority of trials contained inadequate control arms…Even in studies with positive outcomes, effect sizes have been small and the clinical significance of these remains to be established. (Elder & Taylor, 2014, p 8)

Because of this, our *a-priori* power analysis reflects only the treatment of depressive disorders (Sabesan, et al., 2015). For the power analysis, we used the smaller effect size reported by Sabesan and colleagues (Cohen's $d = 0.35$; 2015), as the results would be more conservative. This d value was then converted into a η_p^2 value of .030 for compatibility with the required G*Power procedures using formula found in Cohen (1988, p. 281-285; see Appendix B). The results from this power analysis indicated that our sample would need to consist of at minimum 56 participants, with 28 participants belonging to each of our two analysis groups: (1) individuals meeting MCI criteria, and (2) individuals not meeting MCI criteria. While this study is potentially limited due to the absence of a control, or sham-TMS, group, the non-MCI group will serve as a useful comparison group for the MCI group, as the efficacy of TMS in treating depressive disorders has previously been established among individuals without MCI.

It is important to note that Sabesan and colleagues (2015) reviewed studies that measured depression using the Hamilton Depression Rating Scale (HDRS), not the Beck Depression Inventory II (BDI-II); however, the BDI-II demonstrates strong convergent validity with the HDRS, with a mean correlation of .73 and maximum correlation of up to .89 (Cusin, Yang, Yeung, & Fava, 2009). This strong convergent validity between the two assessments allows us to

generalize the effects and outcomes from the HDRS to the BDI-II for our *a-priori* power analysis.

Instruments

Throughout their treatment sessions, all participants were administered a BDI-II and a Beck Anxiety Inventory (BAI) on a weekly basis, beginning at the start of treatment (i.e. pre-treatment) and continuing through their final treatment session (i.e. post-treatment). Participants were also given three CNS-VS neurocognitive assessments throughout their treatment: one at the start of treatment (i.e. pre-treatment), one at week two of their treatment schedule, and one at the end of treatment (i.e. post-treatment).

Beck Depression Inventory II (BDI-II).

The BDI-II is a 21-item self-report assessment of depressive symptoms. Each item is ranked on a scale of 0-3 based on symptom prevalence in the last week (e.g., "Sadness" can be ranked 0 = *I do not feel sad,* 1 = *I feel sad much of the time,* 2 = *I am sad all the time,* or 3 = *I am so sad or unhappy that I can't stand it*).

Despite the claims made by Hyer, Sohnle, Ashraf, Hamer, and Ragan (2003), stating that the BDI-II and other self-report measures are not appropriate for individuals with cognitive impairment, the BDI-II has been utilized in studies to measure depression in both samples with MCI/dementia and samples without MCI/dementia while retaining adequate psychometric properties (Gilmartin, et al., 2015; Seidel, et al., 2015; Sinanović, Hudić, Zucić, Kapidžić, & Vidović, 2015). For this reason, the BDI-II was utilized for this study.

In a study comparing young adults (n = 229, mean age = 19.6, SD = 2.2) to older adults (n = 147, mean age = 70.3, SD = 7.5), Segal, et al. (2015) found that the BDI-II retains adequate psychometric properties across the two age groups. While there did appear to be a slight decrease

in internal consistency from the young adult group to older adults (α = .92 and α = .86 respectively), the findings support good internal reliability for the BDI-II among older adults.

The BDI-II was also found to be highly correlated with the Geriatric Depression Scale (GDS; r = .71), which is a previously validated measure of depression specifically for older adults (Segal, et al., 2008), and construct validity of the BDI-II has been thoroughly established within the current body of research. For example, Schroevers, Tovote, Snippe, and Fleer (2016) found that mindfulness is as effective as cognitive based therapy at reducing depressive symptoms in individuals as measured by the BDI-II. These results were congruent with their initial hypotheses (Schroevers, et al., 2016).

CNS Vital Signs (CNS-VS).

Computerized neurocognitive screening tools have a major benefit over conventional neurocognitive assessments: computerized assessments are more sensitive and able to detect MCI while in the "preclinical" phase, thus allowing for earlier detection of cognitive decline than conventional assessment measures, such as non-computer-based measures of gross cognitive functioning and dementia screening assessments (Gualtieri, 2004). In fact, "computerized assessment might be uniquely suited to early detection of changes in cognition in the elderly" (Wild, Howieson, Webbe, Seelye, & Kaye, 2008, p. 429).

The CNS Vital Signs (CNS-VS) battery has been used in many studies to assess for MCI and various levels of dementia (Gualtieri, 2004; Gualtieri & Johnson, 2005; Gualtieri & Johnson, 2006; Gualtieri & Johnson, 2008). CNS-VS results have been shown to generate differential profiles for individuals with MCI versus individuals with various levels of dementia (Gualtieri, 2004). CNS-VS has been able to differentiate levels of dementia from other neurological disorders such as post-concussion syndrome, severe traumatic brain injuries, and ADHD. It has

also been shown to differentiate between MCI, dementia, and levels of depression (Gualtieri & Johnson, 2006), which is highly beneficial for the purposes of this study. For these reasons, CNS-VS was deemed an appropriate assessment tool for the context of this study.

CNS-VS is a 30-minute, self-administered, computer-based battery used to assess neurocognitive performance while controlling for age and education. 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-VS 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), and Continuous Performance Test (sustained attention). From these 7 tests, domain scores in the following 10 categories are produced: Neurocognition Index, Composite Memory, Verbal Memory, Visual Memory, Processing Speed, Executive Function, Psychomotor Speed, Reaction Time, Complex Attention, and Cognitive Flexibility (CNS Vital Signs, LLC, 2003).

Studies have produced support for strong reliability with test-retest coefficients ranging from 0.65 to 0.88. Convergent validity comparing the CNS-VS to conventional neuropsychological assessments has been established, with moderate correlations between the CNS-VS and: the Neurobehavioral Evaluation System II (NES2) ranging from $r = .30$ to $r = .60$; Rey Auditory Verbal Learning Test ranging from $r = .49$ to $r = .56$; Logical Memory and Facial Recognition subtests of the Wechsler Memory Test ranging from $r = .35$ to $r = .56$; mechanical finger tapping ranging from $r = .13$ to $r = .26$; Stroop Test with $r = .51$; Trails B with $r = .45$; and the Verbal Fluency Test with $r = .45$ (Gualtieri & Johnson, 2006). While many of these

correlations are moderate in magnitude, it is important to note that many of them may have been attenuated by the lack of common method variance, as many of these are not computerized assessments.

According to Kelly and Peterson (2007), "MCI subjects tend to fall 1.5 standard deviations below their age- and education-matched peers on measurements of learning and recall" (p. 582). It is also noted that these are "guidelines and not cutoff scores for assisting in the diagnosis of MCI" (p. 582). Saykin and Rabin (2014) also stated that MCI can be operationalized as "…decline in neurocognitive test performance, typically between one and two standard deviations below appropriate norms, or 3rd-16th percentile" (p. 240). Regardless of cognitive decline, a key component of MCI is that independence through activities of daily living (ADLs) is typically preserved, even though the use of compensatory strategies and increased effort are often noted (Saykin & Rabin, 2014).

Peterson (2013) defined MCI as the presence of cognitive decline measured in a single cognitive domain while independence is preserved. When multiple cognitive domains show significant impairment and loss of independence is noted, a diagnosis of dementia, or MND, is more appropriate. Declines in cognitive domains can be assessed in many ways: formal and informal assessments of the individual providing the complaint, informal assessments of reputable sources close to the individual in question, and computerized cognitive batteries (Peterson, 2013; Saykin & Rabin, 2014).

MCI is typically categorized into two subtypes: amnestic MCI and non-amnestic MCI, which are defined as cognitive impairments with the presence or absence of memory impairments respectively (Peterson, 2007). Even further, both amnestic MCI and non-amnestic MCI can be further defined as single-domain and multiple-domain. While MCI usually appears

with only one major cognitive domain (outside of memory complaints) impaired, it is possible to find cases of MCI in which multiple domains are impaired (Peterson, 2007), as long as independence and ADL ability are still widely maintained (Peterson, 2007; Peterson, 2013; Saykin & Rabin, 2014). These findings have also been established in a report by the Alzheimer's Association in defining the clinical diagnosis of MCI (Albert, et al., 2010).

Because it appears that no one specific cognitive domain is impaired across MCI diagnoses, with the exception of memory in amnestic-MCI, the operationalization of MCI for the purpose of this study was as follows: CNS-VS scores indicating an individual being at least one standard deviation below their age- and education-based norms on at least one cognitive domain. To increase the power of this study, amnestic and non-amnestic MCI were defined separately in the analyses. The CNS-VS was then used to track cognitive changes throughout treatment among the two groups: (1) participants meeting MCI criteria and (2) participants not meeting MCI criteria. This methodology is supported by Harvey (2012): "It makes sense that the same measures of cognitive functioning used to identify functionally relevant deficits across different neuropsychiatric conditions would be used to measure treatment outcomes" (p. 96).

Beck Anxiety Inventory (BAI).

The Beck Anxiety Inventory (BAI) was used in this study as a means of measuring and covarying anxiety from our statistical model, as depression and anxiety are positively correlated when measured together ($r > .50$; Beck, Epstein, Brown, & Steer, 1988, p. 893). The BAI is a 21-item self-report measure designed to assess for anxiety, with each item being scored on a 4-point scale based on the prevalence of specific anxiety-related symptoms within the last week (e.g., "Nervousness" can be ranked 0 = *Not at All;* 1 = *Mildly;* 2 = *Moderately;* 3 = *Severely*). The BAI has demonstrated good test-retest reliability, with $r = .75$, and sound internal

consistency, with Cronbach's α = .92 (Beck, Ebstein, Brown, & Steer, 1988, p. 895). Convergent validity of the BAI has been established with the Hamilton Anxiety Rating Scale, a previously established measure of anxiety, with coefficients ranging from .47 to .58 (Grant, n.d., p. 2). The construct validity of the BAI has been well established in the literature. For example, Potes, Gagnon, Touré, and Perreault (2016) found that psychoeducational programs improve symptoms of anxiety among individuals. These results were congruent with their initial hypotheses (Potes, et al., 2016).

No studies could be found assessing the psychometric properties of the BAI among cognitively impaired populations. However, the BAI has been used to assess anxiety among geriatric populations, age 60 years and older, and it has remained psychometrically sound. Test-retest coefficients among geriatric individuals ranged from .62 (seven-week interval) to .93 (one-week interval), and Cronbach's α ranged from .90 to .94 (Potes, et al., 2016, p. 653). It should be noted that this study by Potes, and colleagues (2016) excluded individuals with MCI, assessed by scores less than 28 on the Mini-Mental Status Exam (MMSE).

Procedures

Individuals seeking treatment in the Eastern Virginia Medical School (EVMS) TMS program underwent 36 treatment sessions. Each session lasted approximately 40 minutes and occurred five days per week for six weeks, followed by a three-week taper which spaced out the remaining sessions over the three-week period (e.g., three TMS sessions during the seventh week, two sessions during the eighth week, and one session during the ninth week). Individuals may receive extra TMS sessions, deemed "maintenance sessions," if needed after the initial treatment schedule. For the scope of this study, we focused on the 36 initial sessions only.

All participants in the EVMS TMS treatment program were evaluated for the presence of treatment-resistant, or refractory, depression. Depressive disorder diagnoses are deemed treatment-resistant when antidepressant medications in adequate doses/intensities trialed over sufficient time to produce treatment responses have failed to produce remission in depressive symptoms (Chappell, 2016). To date, ECT has been the primary treatment modality for treatment-resistant depression; however, there appears to be considerable research consensus that TMS/rTMS is not only equally efficacious in comparison to ECT, but also more cost-effective, patient-preferred, and less risky (Magnezi, et al., 2016; U.S. DHHS, FDA, & CDRH, 2011).

Prior to the first TMS treatment session, the patient's resting motor threshold (RMT) was established to ensure precision of stimulation. RMTs were determined by applying single magnetic pulses over the right motor cortex area until a twitch in the contralateral hand was achieved. Participants over the age of 70 also underwent neuroimaging procedures in order to measure any cortical atrophy.

Upon intake, participants were evaluated for the presence of depressive disorders and/or anxiety disorders. Individuals with only depressive disorders (e.g., major depressive disorder without anxious features) were assigned to the left TMS protocol. Individuals with depressive disorders and clinically elevated levels of anxiety were assigned to the right TMS protocol. The left protocol targeted the left dorsolateral prefrontal cortex (LDLPFC), and it is widely considered the most commonly used location for stimulation in TMS when treating depressive disorders only (Herbsman, et al., 2009; Teng, et al., 2017). Studies using EEGs to measure brain activity among individuals with major depressive disorder have revealed asymmetrical activity levels in the DLPFC (Ricardo-Garcell, et al., 2009). TMS studies targeting both the right and the

left DLPFC have produced positive outcomes in reducing depressive symptomology (Teng, et al., 2017).

The right protocol targeted the right dorsolateral prefrontal cortex (RDLPFC) as well as the right supplementary motor area (SMA), and it is primarily used for individuals with depressive disorders as well as clinically elevated levels of anxiety, history of trauma, or obsessive-compulsions. Similar to the LDLPFC, stimulating the RDLPFC is also associated with improvements in depressive symptomology (Luber, et al., 2017). The right SMA has been studied with TMS in managing anxiety-related symptoms (e.g., anxiety disorders, PTSD, and OCD; Fontenelle, Nascimento, Mendlowicz, Shavitt, & Versiani, 2007; Machado, et al., 2013; Mantovani, n.d.; Mantovani, Simpson, Fallon, Rossi, & Lisanby, 2010), treating cognitive impairments and depressive symptoms among individuals with VaD with successful outcomes (Pennisi, et al., 2016), as well as specifically improving visual-spatial processing (Cona, Marino, & Semenza, 2017).

Individuals who received the right TMS protocol received 1,200 pulses at 1Hz, 110% RMT to the RDLPFC for 20 minutes and 8 seconds and 1,200 pulses at 1Hz, 100% RMT to the right SMA for 20 minutes and 8 seconds, with stimulations being delivered in 1-second pulses at each area for a total duration of 40 minutes and 16 seconds each session. Individuals who received the left TMS protocol received 3,000 pulses at between 5 and 20 Hz, 120% RMT to the LDLPFC, with stimulations being delivered 10 pulses per second for four seconds with a 26-second pause in stimulation for each train of pulses, totaling to 37 minutes and 40 seconds each session.

During their treatment schedules, participants complete the BDI-II and BAI once per week, including pre- and post-treatment measurements. The CNS-VS is administered three times during the treatment schedule: pre-treatment, two weeks into treatment, and post-treatment.

Design and Statistical Analysis

The effects of TMS on depressive symptomology and neurocognitive performance were evaluated over time. Treatment data was taken from multiple time-points during the treatment schedule: pre-treatment, week two of treatment, and post-treatment. Utilizing multiple time points also reduced the risk of regression toward the mean.

The statistical analysis procedures for this study consisted of the following: (1) a repeated measures split-plot ANOVA (time: baseline, two weeks, post-treatment; cognitive function groups: 0 = MCI, 1 = non-MCI) on BDI-II scores. This would show changes in depression levels across time, and if these differences over time are different between the two cognitive function groups; (2) a series of repeated measures split-plot ANOVA (time: baseline, two weeks, post-treatment; cognitive function groups: 0 = MCI, 1 = non-MCI) on CNS-VS scores, which would show cognitive changes among individuals with cognitive impairment versus individuals without cognitive impairment over time; (3) a regression model regressing the CNS-VS scores onto the BDI-II scores. The residual values from this regression model represented the CNS-VS scores while holding depression (BDI-II scores) constant; and (4) a third series of repeated measures split-plot ANOVA (time: baseline, two weeks, post-treatment; cognitive function groups: 0 = MCI, 1 = non-MCI) on the residual CNS-VS values from the above regression analysis. This would show cognitive changes as a result of TMS treatment above and beyond any depression changes.

IRB Submissions

This study was submitted to the Institutional Review Boards (IRBs) of both Eastern Virginia Medical School (EVMS) and Old Dominion University (ODU). EVMS served as the primary reviewer, as the data was being extracted from a previously approved registry database created and maintained at EVMS. EVMS approved the study on January 16, 2018 (IRB Approval #: 17-12-WC-0293-EVMS). ODU subsequently approved this research study on February 6, 2018 (IRB Approval #: 1184323-1).

Results

Data Reduction and Data Cleaning

The registry database contained a total of 95 participants. For the purpose of this study, though, participants were excluded from the analyses if they met any of the following criteria: (1) they did not initiate or complete their course of treatment, (2) they did not have a diagnosis of MDD at the time of referral, or (3) they were not diagnosed with MDD during the pre-treatment evaluations. Of the 95 total participants, five received an initial evaluation but did not initiate treatment. An additional 12 participants started TMS treatment but did not complete the entire 36 treatment sessions. Of the remaining participants who completed treatment, 10 did not have a primary diagnosis of MDD, nor were they diagnosed with MDD at the initial evaluations. As a result, 27 total participants were excluded from this research study, leaving a total sample of 68 participants ($N = 68$).

Participants were then classified as either meeting MCI criteria (0) or not meeting MCI criteria (1). Of the 68 participants included in this study, 38 met the previously outlined MCI criteria (i.e. baseline CNS-VS scores indicating below average performance on at least one cognitive domain) and 30 did not meet MCI criteria (i.e. baseline CNS-VS scores indicating all

cognitive domains at least within average range). Based on the results from the *a-priori* power analysis, this research study does meet pre-determined sample-size criteria for statistical power.

Each dependent variable was screened for skewness and kurtosis statistics in order to assess the ANOVA assumption of normality. According to Skeskin (2011), both skewness and kurtosis statistics are considered within normal limits if their absolute value is less than 1.96; as a result, this benchmark was used to assess normality of distribution in the dependent variables. Table 1 shows the skewness and kurtosis statistics of each dependent variable. Based on these results, many of the dependent variables did not meet criteria for normal distribution.

Table 1

Skewness and Kurtosis Statistics

Variable Name	*N*	Skewness	Kurtosis
BDI-II Baseline	68	-0.37	-0.27
BDI-II Week 2	68	0.24	-0.78
BDI-II End-of-Treatment	68	0.69	-0.84
CNS-VS Neurocognition Index, Baseline	68	-1.79	**4.11**
CNS-VS Composite Memory, Baseline	68	-0.64	0.73
CNS-VS Verbal Memory, Baseline	68	-0.73	0.03
CNS-VS Visual Memory, Baseline	68	-0.40	-0.26
CNS-VS Processing Speed, Baseline	68	0.07	0.93
CNS-VS Executive Functioning, Baseline	68	-1.53	**3.40**
CNS-VS Psychomotor Speed, Baseline	68	-0.79	**3.82**

CNS-VS Reaction Time, Baseline	68	-0.16	**2.32**
CNS-VS Complex Attention, Baseline	68	**-4.53**	**26.60**
CNS-VS Cognitive Flexibility, Baseline	68	-1.46	**2.83**
CNS-VS Neurocognition Index, Week 2	68	-1.22	**2.18**
CNS-VS Composite Memory, Week 2	68	-0.44	0.70
CNS-VS Verbal Memory, Week 2	68	-0.60	-0.20
CNS-VS Visual Memory, Week 2	68	-0.31	0.21
CNS-VS Processing Speed, Week 2	68	0.18	-0.32
CNS-VS Executive Functioning, Week 2	68	-1.55	**3.49**
CNS-VS Psychomotor Speed, Week 2	68	-0.09	**2.15**
CNS-VS Reaction Time, Week 2	68	-0.52	**16.02**
CNS-VS Complex Attention, Week 2	68	**-3.74**	**2.61**
CNS-VS Cognitive Flexibility, Week 2	68	-1.40	**6.99**
CNS-VS Neurocognition Index, End-of-Treatment	68	-1.85	1.43
CNS-VS Composite Memory, End-of-Treatment	68	-0.87	**2.96**
CNS-VS Verbal Memory, End-of-Treatment	68	-1.41	-0.53
CNS-VS Visual Memory, End-of-Treatment	68	-0.09	**2.57**
CNS-VS Processing Speed, End-of-Treatment	68	-1.04	**11.44**
CNS-VS Executive Functioning, End-of-Treatment	68	**-2.48**	**2.00**
CNS-VS Psychomotor Speed, End-of-Treatment	68	0.33	**2.35**
CNS-VS Reaction Time, End-of-Treatment	68	-1.24	**10.67**
CNS-VS Complex Attention, End-of-Treatment	68	**-3.14**	**10.47**
CNS-VS Cognitive Flexibility, End-of-Treatment	68	**-2.44**	-0.27

Analysis of the data, via box-plots and interquartile range calculations, showed a significant number of outliers. While no multivariate outliers were detected within the data, many univariate outliers were present. This likely influenced the distribution of the data, leading to the extreme skewness/kurtosis values seen in Table 1. According to Jamaluddin, Abdullah, and Yahaya (2014), winsorization of extreme outliers is an appropriate approach to managing univariate outliers, especially when they are causing non-normality in variable distributions. Based on this information, the winsorization approach was used to treat univariate outliers in the dependent variable data. After winsorization, all variables fell within normal limits in both skewness and kurtosis values (i.e. below absolute value of 1.96; Skeskin, 2011). Typical procedures dictate that data analyses should be run both before and after correction of outliers; however, because the normality of variables was violated to such an extreme level before treating for outliers, data analyses would not be reliable; as a result, the data were only analyzed after treating for outliers. All other ANOVA assumptions were met.

Sample Demographics

All participants in this research study (N = 68) completed TMS treatment. Participants were separated into two groups (MCI and non-MCI) based on the pre-determined criteria. Demographic information was obtained for each group in the following areas: age, baseline BAI score, baseline BDI-II score, type of TMS protocol, and education level. Analyses were run on the demographics variables to determine any significant differences between the MCI and non-MCI groups: age differences were nonsignificant, with $t(66) = 1.61$, $p = .113$ (see Table 2); sex differences were nonsignificant, with $\chi^2(1) = 0.21$, $p = .649$ (see Table 2); baseline BAI scores were nonsignificant, with $t(66) = 0.87$, $p = .388$ (see Table 2); baseline BDI-II scores were

nonsignificant, with $t(66) = 1.12$, $p = .268$ (see Table 2); type of TMS protocol between groups was nonsignificant, with $\chi^2(1) = 2.38$, $p = .123$ (see Table 2); and education level between groups was nonsignificant, with $\chi^2(7) = 5.23$, $p = .608$ (see Table 2). Because these variables were not significantly different between the groups, there was no empirical rationale to use them as covariates in the statistical model. As such, these variables will not be used as covariates in this study.

Table 2

Demographic Information by Group

		N	*Mean*	*SD*
MCI	Age	38	47.76	14.03
	Baseline BAI Scores	38	18.45	11.84
	Baseline BDI-II Scores	38	34.71	12.17
Non-MCI	Age	30	42.17	14.52
	Baseline BAI Scores	30	21.70	12.05
	Baseline BDI-II Scores	30	37.00	8.74
Total	Age	68	45.29	14.41
	Baseline BAI Scores	68	19.88	11.92
	Baseline BDI-II Scores	68	35.72	10.78

	N (%)		
	Left TMS Protocol	Right TMS Protocol	Total *N* (%)
MCI	11 (16.18)	27 (39.71)	38 (55.88)
Non-MCI	4 (5.88)	26 (38.24)	30 (44.12)

Total	15 (22.06)	53 (77.94)	68 (100.00)

		N	%
MCI	Males	16	23.53
	Females	22	32.35
	Total (sex)	38	55.88
	High School / GED	7	10.61
	Some College	7	10.61
	Trade School / Certificate	1	1.52
	2-Year College Degree	5	7.58
	4-Year College Degree	7	10.61
	Master's Degree	7	10.61
	Doctoral Degree	1	1.52
	Professional Degree (MD, JD)	1	1.52
	Total (edu)	36	54.55
Non-MCI	Males	11	16.18
	Females	19	27.94
	Total (sex)	30	44.12
	High School / GED	3	4.55
	Some College	7	10.61
	Trade School / Certificate	0	0.00
	2-Year College Degree	2	3.03
	4-Year College Degree	11	16.67
	Master's Degree	4	6.06

	Doctoral Degree	2	3.03
	Professional Degree (MD, JD)	1	1.52
	Total (edu)	30	45.45
Total	Males	27	39.71
	Females	41	60.29
	Total (sex)	68	100.00
	High School / GED	10	15.15
	Some College	14	21.21
	Trade School / Certificate	1	1.52
	2-Year College Degree	7	10.61
	4-Year College Degree	18	27.27
	Master's Degree	11	16.67
	Doctoral Degree	3	4.55
	Professional Degree (MD, JD)	2	3.03
	Total (edu)	66	100.00

Reliability of Measures

Reliability via internal consistency (Cronbach's α) of the BDI-II and the BAI was assessed at each time point (baseline, week two, end-of-treatment). The BDI-II demonstrated strong internal consistency at all time points in the total sample, with baseline α = .89, week two α = .92, and end-of treatment α = .96. The BAI also demonstrated strong internal consistency across all time points in the total sample, with baseline α = .91, week two α = .93, and end-of-

treatment α = .95. Both measures also demonstrated strong internal consistency within the MCI group, with BDI-II baseline α = .91, week two α = .92, and end-of-treatment α = .95, and BAI baseline α = .87, week two α = .92, and end-of-treatment α = .92. For the non-MCI group, internal consistency statistics were good-to-strong, with BDI-II baseline α = .77, week two α = .86, and end-of-treatment α = .95, and BAI baseline α = .92, week two α = .92, and end-of-treatment α = .96.

Research Question 1

The first research question investigated in this study was as follows: can TMS be used effectively to treat depression in patients with MCI? The resulting hypothesis was that TMS treatment will improve depression levels significantly among individuals meeting MCI criteria, and that any improvements here will not be significantly different from improvements seen in the non-MCI group – in other words, TMS treatment should be equally effective for both the MCI and non-MCI groups.

This hypothesis was tested using a repeated measures split-plot ANOVA (time: baseline, two weeks, post-treatment; cognitive function groups: 0 = MCI, 1 = non-MCI) on BDI-II scores in order to show any treatment differences between the cognitive function groups on depression. Familywise alpha was set to .05 and did not need further correction, as this ANOVA falls under its own family of tests.

Sphericity could not be assumed, with Mauchly's $\chi^2(2) = 17.05$, $p < .001$. As a result, Greenhous-Geisser's correction of sphericity was used, with $\hat{\varepsilon} = .81$. Greenhouse-Geisser's correction was chosen over Huynh-Feldt as it is a more conservative correction of sphericity than Hyunh-Feldt. The treatment/time effect showed significant changes in depressive symptoms from start-to-end of treatment, with $F(1.63, 107.26) = 77.41$, $p < .001$, $\eta_p^2 = .540$ (see *Figure 1*).

Post-hoc pairwise comparisons between each time interval (baseline, week two, end of treatment) were performed using Bonferroni comparisons. Type 1 error (alpha) was corrected here using Bonferroni's alpha correction formula, $\alpha_{PC} = \alpha/C$ (Maxwell & Delaney, 2004, p. 202), where $\alpha = .05$ and $C = 3$. The resulting alpha per contrast resulted: $\alpha_{PC} = .0167$. The following follow-up pairwise comparisons were significant at the corrected α_{PC}: baseline-to-week-two, with $MD = 13.26$, $SE = 1.27$, $p < .001$, 95% CI [10.14, 16.38]; baseline-to-end-of-treatment, with $MD = 18.78$, $SE = 1.88$, $p < .001$, 95% CI [14.17, 23.40]; and week-two-to-end-of-treatment, with $MD = 5.53$, $SE = 1.44$ $p = .001$, 95% CI [1.99, 9.07]. The group-by-time differences were not significant, with $F(1.63, 107.26) = 0.27$, $p = .721$, $\eta_p^2 = .004$ (see *Figure 1*), indicating no significant differences between the MCI and non-MCI groups on depressive symptom improvement.

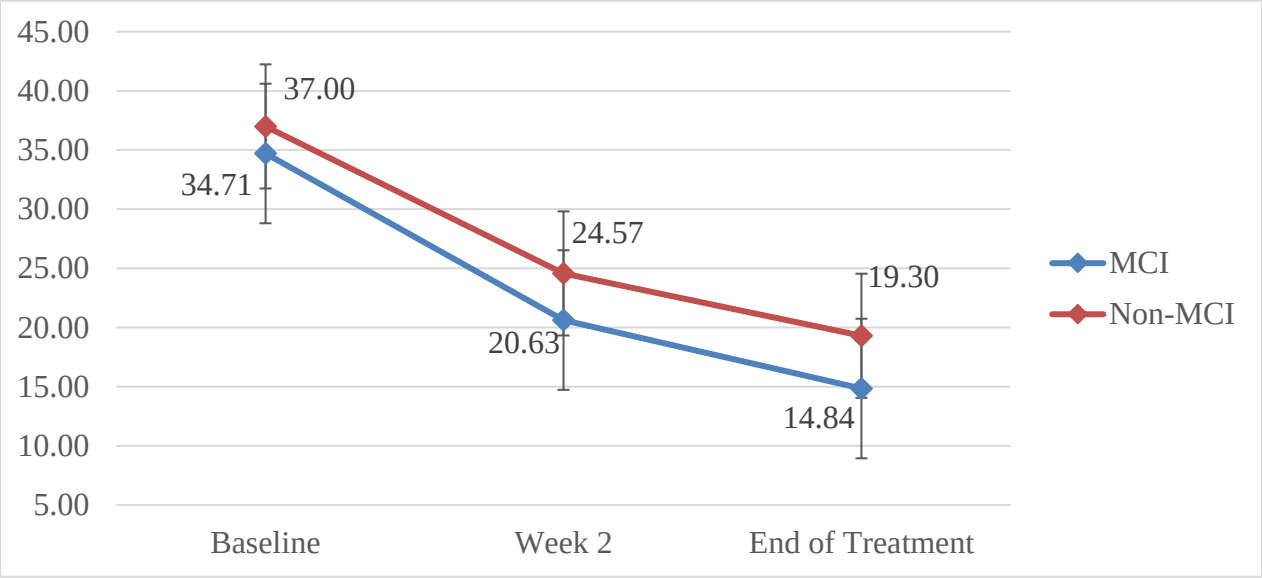


Figure 1. Depressive Symptom Improvement (BDI-II) between MCI and Non-MCI Groups

Research Question 2

The second research question investigated in this study was as follows: can TMS be used to improve cognitive functioning among individuals with MCI independent of mood improvements? The resulting hypothesis was that TMS treatment will produce significant improvements in neurocognitive functioning among individuals with MCI, and that these improvements will remain significant after controlling for the variance of improvements in depressive symptoms.

This hypothesis was tested using multiple repeated measures split-plot ANOVAs (time: baseline, two weeks, post-treatment; cognitive function groups: 0 = MCI, 1 = non-MCI) on CNS-VS domain scores in order to show any treatment differences among different neurocognitive domains. Familywise error was set at .05. Given that 10 repeated measures split-plot ANOVAs were performed (one for each neurocognitive domain dependent variable), error per comparison was corrected using Bonferroni's alpha correction formula, $\alpha_{PC} = \alpha/C$ (Maxwell & Delaney, 2004, p. 202), where $\alpha = .05$ and $C = 10$. The resulting alpha per contrast resulted: $\alpha_{PC} = .005$. Where significant treatment/time effects were found, post-hoc pairwise comparisons were analyzed using Bonferroni comparisons, and the Type 1 error rate was corrected further, with Bonferroni's alpha correction formula, $\alpha_{PC} = \alpha/C$ (Maxwell & Delaney, 2004, p. 202), where $\alpha = .005$ and $C = 3$. The resulting corrected error per contrast was $\alpha_{PC} = .0017$. In any situations in which sphericity could not be assumed, Greenhous-Geisser's correction of sphericity was used, as it is the more conservative correction method.

For Neurocognition Index (NCI), sphericity could not be assumed, with $\chi^2(2) = 13.01$, $p = .001$, with $\hat{\mathcal{E}} = .85$. The treatment/time effect was significant, with $F(1.69, 111.74) = 20.14$, $p <$

.001, η_p^2 = .234. The group-by-time was also significant, with $F(1.69, 111.74) = 8.34$, p = .001, η_p^2 = .112, indicating a difference MCI and non-MCI groups on NCI (see *Figure 2*).

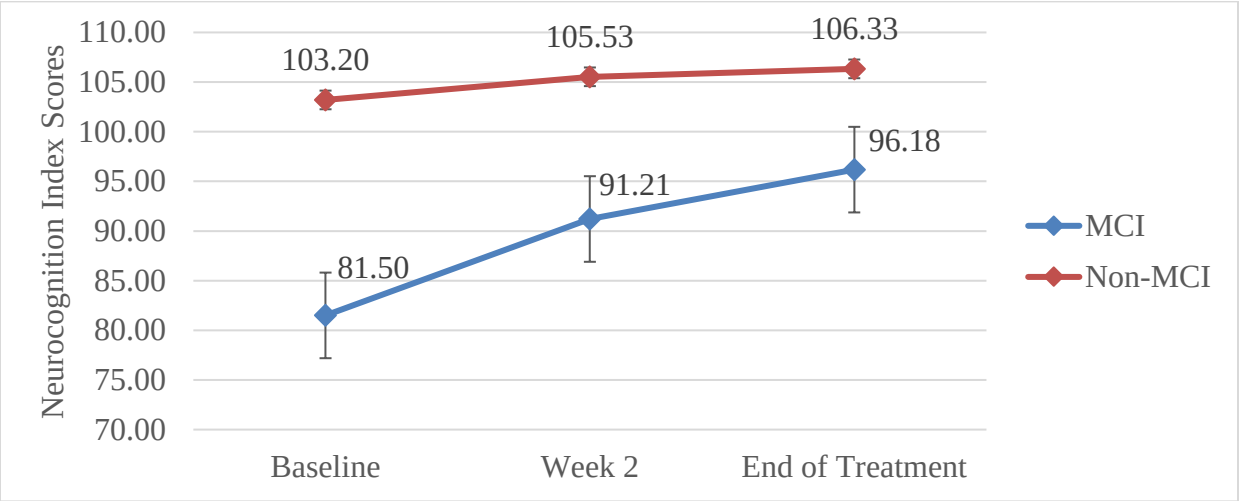


Figure 2. Neurocognition Index Improvement between MCI and non-MCI Groups

For Composite Memory (CM), sphericity was assumed, with $\chi^2(2) = 1.19$, p = .551. The treatment/time effect on CM changes was not significant, with $F(2, 132) = 1.87$, p = .158, η_p^2 = .028 (see *Figure 3*). For Verbal Memory (VERM), sphericity was assumed, with $\chi^2(2) = 5.82$, p = .055. The treatment/time effect on VERM changes was not significant, with $F(2, 132) = 3.06$, p = .050, η_p^2 = .044 (see *Figure 4*). For Visual Memory (VISM), sphericity was assumed, with $\chi^2(2) = .54$, p = .765. The treatment/time effect on VISM changes was not significant, with $F(2, 132) = .72$, p = .487, η_p^2 = .011 (see *Figure 5*). No further follow-up tests for CM, VERM, or VISM were performed.

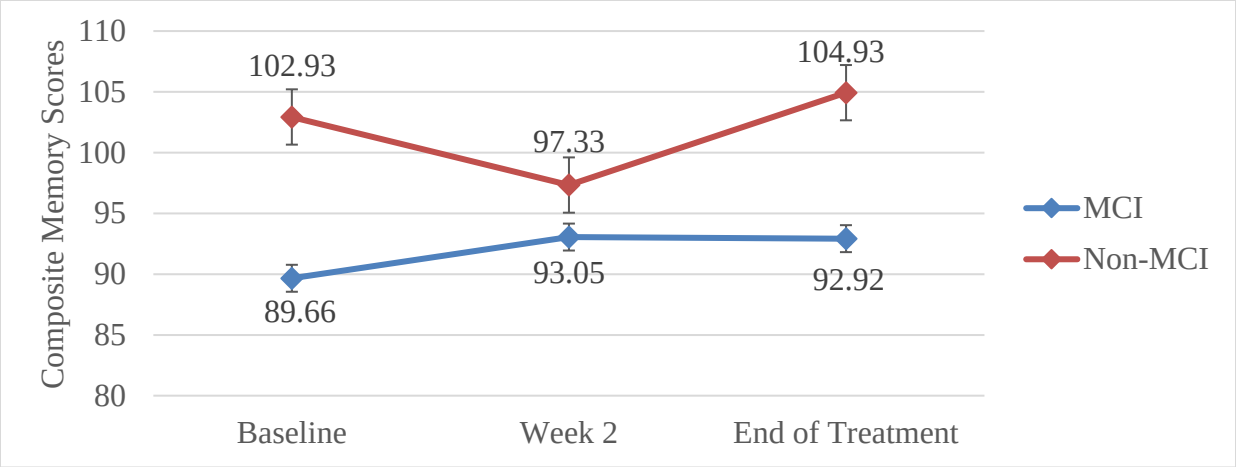


Figure 3. Composite Memory Improvement between MCI and Non-MCI Groups

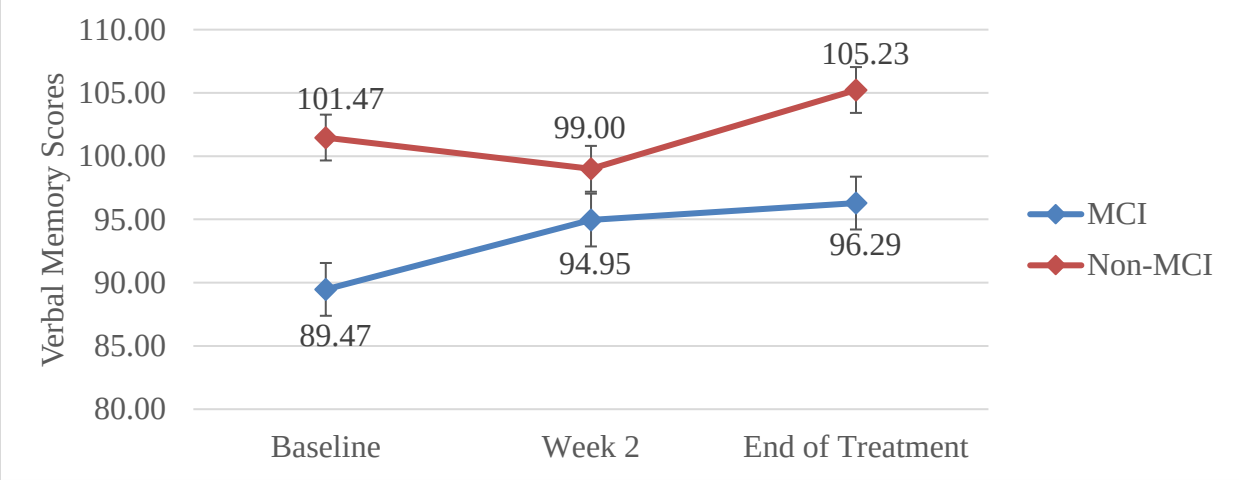


Figure 4. Verbal Memory Improvement between MCI and Non-MCI Groups

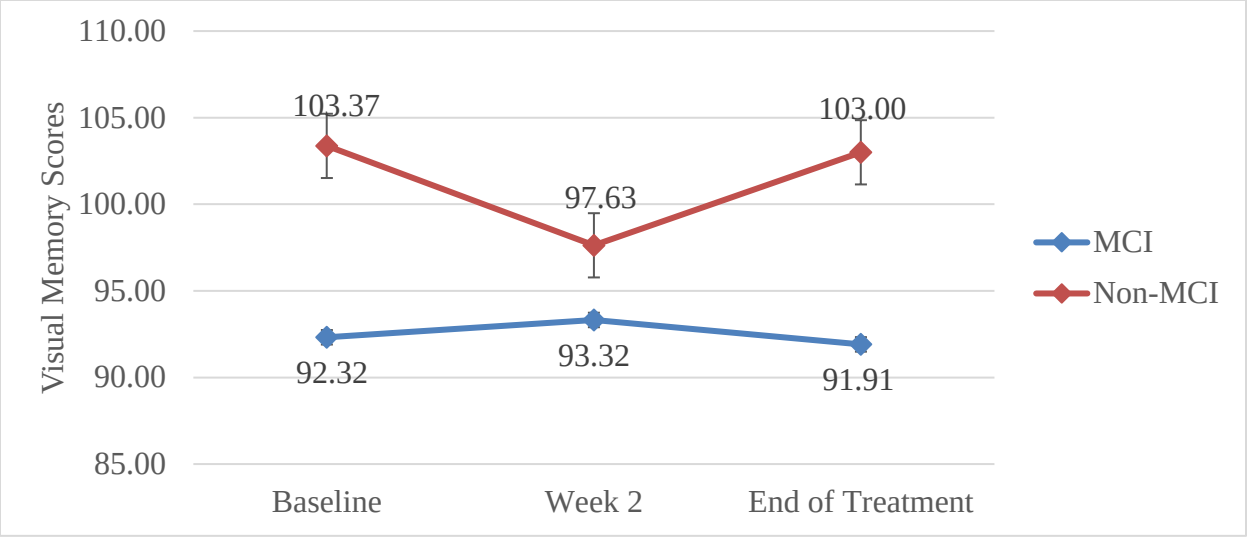


Figure 5. Visual Memory Improvement between MCI and Non-MCI Groups

For Processing Speed (PROSS), sphericity could not be assumed, with $\chi^2(2) = 7.03$, $p = .030$, with $\hat{\varepsilon} = .91$. The treatment/time effect was significant, with $F(1.81, 119.73) = 20.21$, $p < .001$, $\eta_p^2 = .234$. The group-by-time was not significant, with $F(1.81, 119.73) = 1.22$, $p = .297$, $\eta_p^2 = .018$, indicating no difference MCI and non-MCI groups on PROSS changes (see *Figure 6*).

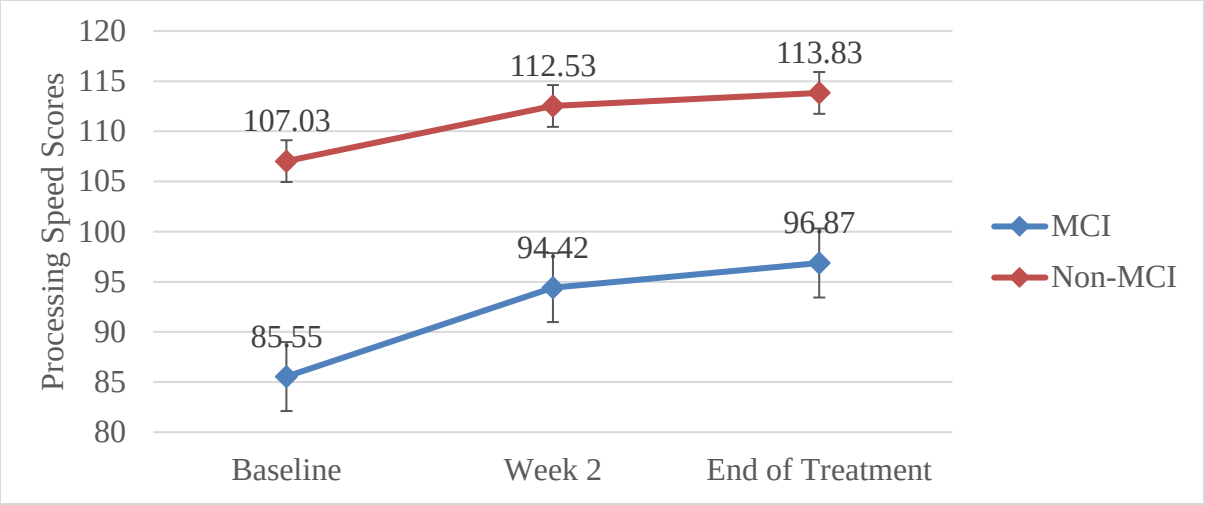


Figure 6. Processing Speed Improvement between MCI and Non-MCI Groups

For Executive Function (EF), sphericity could not be assumed, with $\chi^2(2) = 9.30$, $p = .010$, with $\hat{\varepsilon} = .88$. The treatment/time effect was significant, with $F(1.77, 116.47) = 26.82$, $p < .001$, $\eta_p^2 = .289$. The group-by-time was significant, with $F(1.77, 116.47) = 7.96$, $p = .001$, $\eta_p^2 = .108$, indicating a significant difference between MCI and non-MCI groups on EF changes (see *Figure 7*).

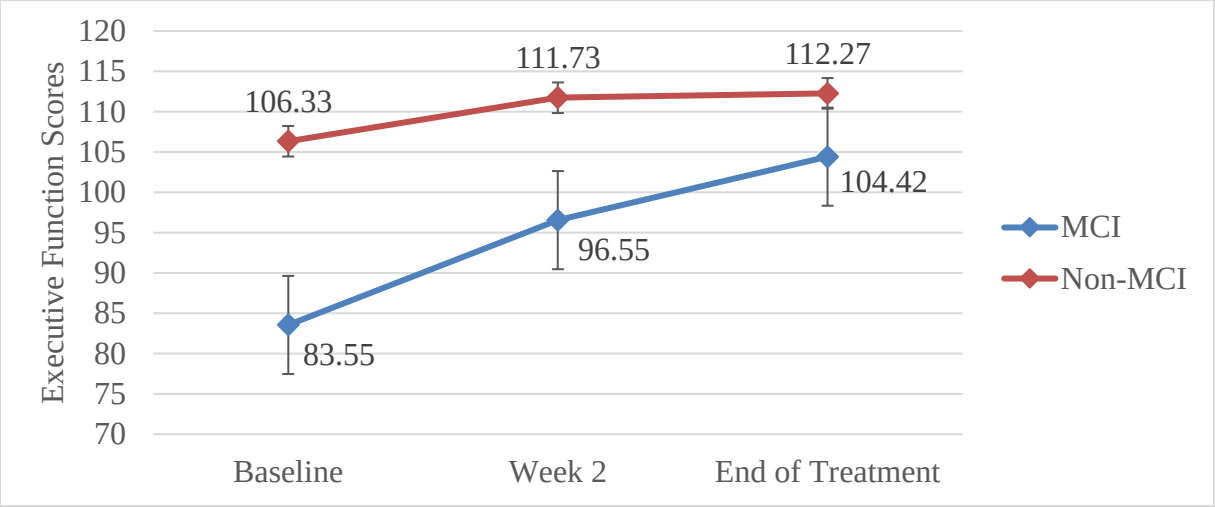


Figure 7. Executive Function Improvement between MCI and Non-MCI Groups

For Psychomotor Speed (PSYS), sphericity could not be assumed, with $\chi^2(2) = 9.32$, $p = .009$. with $\hat{\mathcal{E}} = .88$. The treatment/time effect was significant, with $F(1.76, 116.44) = 18.68$, $p < .001$, $\eta_p^2 = .221$. The group-by-time was not significant, with $F(1.76, 116.44) = 0.61$, $p = .524$, $\eta_p^2 = .009$, indicating no difference in treatment progression between MCI and non-MCI groups (see *Figure 8*).

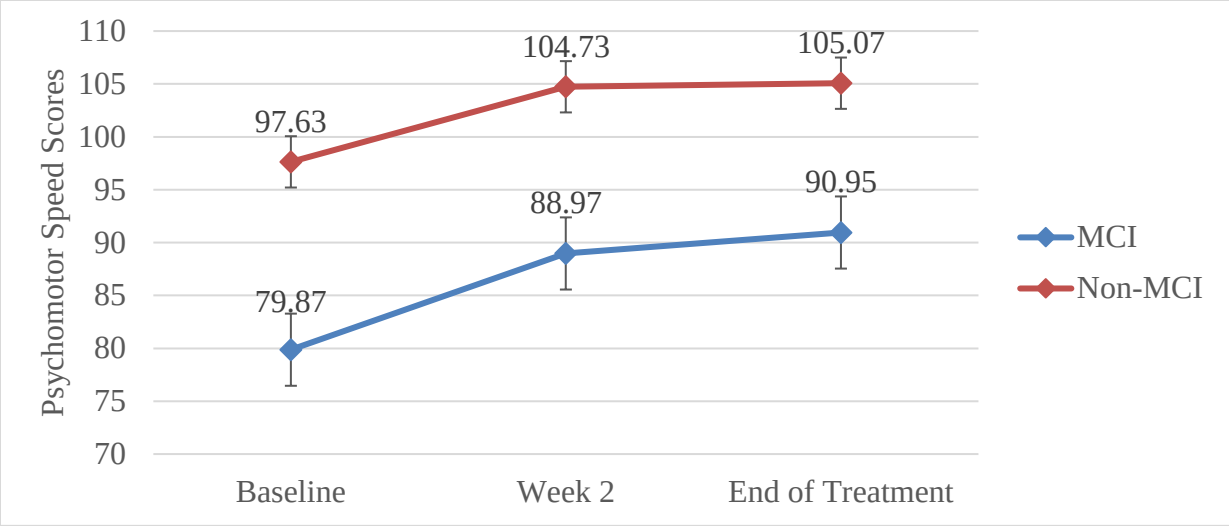


Figure 8. Psychomotor Speed Improvement between MCI and Non-MCI Groups

For Reaction Time (RT), sphericity was assumed, with $\chi^2(2) = 5.16$, $p = .076$. The treatment/time effect was not significant, with $F(2, 132) = 1.14$, $p = .323$, $\eta_p^2 = .017$. No further follow-up testing for RT was performed (see *Figure 9*).

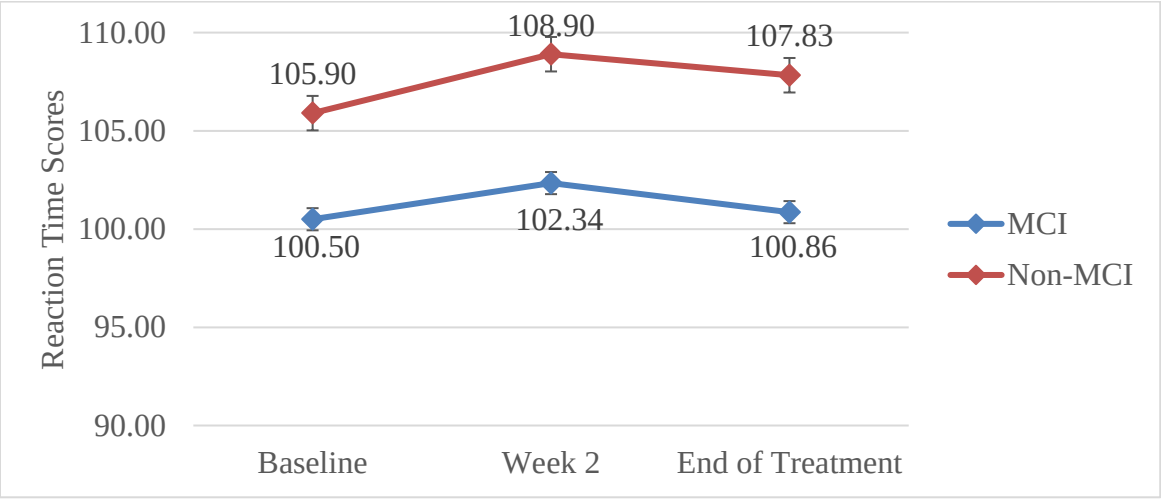


Figure 9. Reaction Time Improvements between MCI and Non-MCI Groups

For Complex Attention (CA), sphericity could not be assumed, with $\chi^2(2) = 11.75$, $p = .003$, with $\hat{\epsilon} = .86$. The treatment/time effect was significant, with $F(1.72, 113.27) = 15.57$, $p < .001$, $\eta_p^2 = .191$. The group-by-time was significant, with $F(1.72, 113.27) = 10.96$, $p < .001$, $\eta_p^2 = .142$, indicating a significant difference in treatment progression between MCI and non-MCI groups (see *Figure 10*).

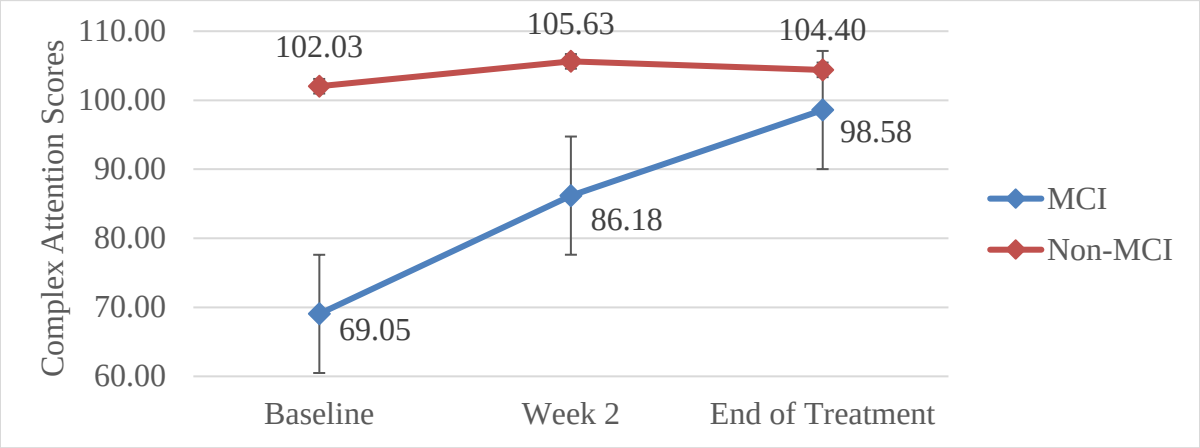


Figure 10. Complex Attention Improvement between MCI and Non-MCI Groups

For Cognitive Flexibility (CF), sphericity could not be assumed, with $\chi^2(2) = 8.63$, $p = .013$, with $\hat{\epsilon} = .89$. The treatment/time effect was significant, with $F(1.78, 117.41) = 28.43$, $p < .001$, $\eta_p^2 = .301$. The group-by-time was significant, with $F(1.78, 117.41) = 8.71$, $p = .001$, $\eta_p^2 = .117$, indicating a significant difference in treatment progression between MCI and non-MCI groups (see *Figure 11*).

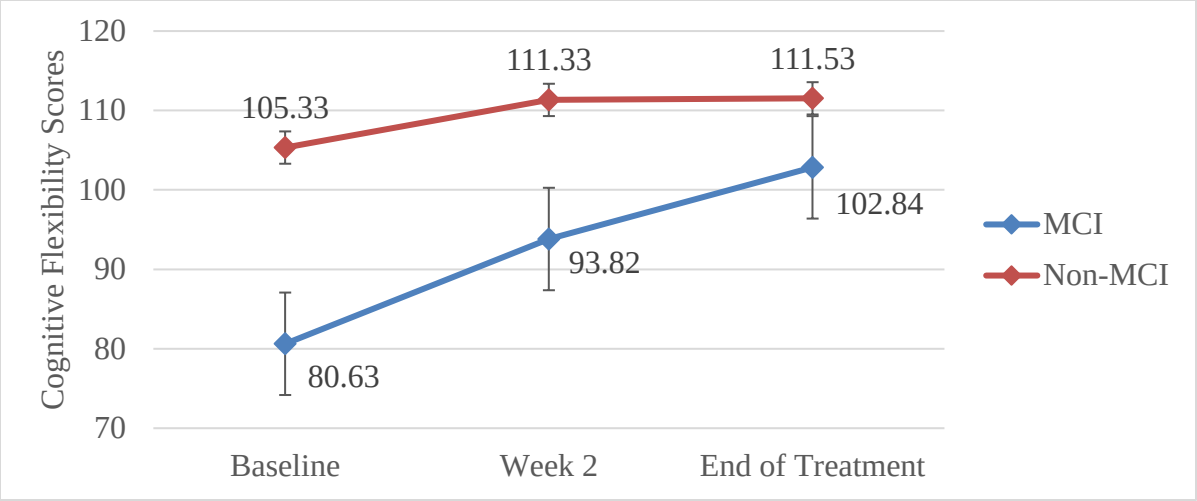


Figure 11. Cognitive Flexibility Improvement between MCI and Non-MCI Groups

Table 3

ANOVAs: TMS on Neurocognitive Performance between MCI and Non-MCI Groups

		df	Mean Square	*F*	η_p^2
NCI	TMS Treatment Over Time	1.69	16363.75	20.14**	.234
	Group X Time	1.69	677.55	8.34*	.112
	Error	111.74	81.25		
CM	TMS Treatment Over Time	2	246.84	1.87	.028
	Group X Time	2	397.54	3.02	.044
	Error	132	131.69		
VERM	TMS Treatment Over Time	2	498.52	3.06	.044
	Group X Time	2	268.99	1.65	.024
	Error	132	132.98		
VISM	TMS Treatment Over Time	2	108.30	0.72	.011

	Group X Time	2	254.42	1.70	.025
	Error	132	148.56		
PROSS	TMS Treatment Over Time	1.81	1690.17	20.21**	.234
	Group X Time	1.81	101.83	1.22	.018
	Error	119.73	83.63		
EF	TMS Treatment Over Time	1.77	3570.43	26.82**	.289
	Group X Time	1.77	1059.65	7.96*	.108
	Error	116.47	133.12		
PSYS	TMS Treatment Over Time	1.76	1934.20	18.68**	.221
	Group X Time	1.76	63.36	0.61	.009
	Error	116.40	103.57		
RT	TMS Treatment Over Time	2	98.32	1.14	.017
	Group X Time	2	10.77	0.13	.002
	Error	132	86.36		
CA	TMS Treatment Over Time	1.72	5117.20	15.57**	.191
	Group X Time	1.72	3602.87	10.96**	.142
	Error	113.27	328.68		
CF	TMS Treatment Over Time	1.78	3959.18	28.43**	.301
	Group X Time	1.78	1212.13	8.71*	.117
	Error	117.41	139.25		

* $p < .005$ (corrected error rate, Bonferroni)

** $p < .001$

Table 4

Significant Post-Hoc Pairwise Comparisons among Significant CNS-VS Domain Improvements

					95% CI	
			MD	*SE*	Lower Bound	Upper Bound
NCI	Baseline	Week 2	-6.02**	1.25	-9.09	-2.95
		End of Treatment	-8.91**	1.71	-13.11	-4.71
PROSS	Baseline	Week 2	-7.18**	1.34	-10.48	-3.89
		End of Treatment	-9.06**	1.73	-13.30	-4.82
EF	Baseline	Week 2	-9.20**	1.76	-13.51	-4.89
		End of Treatment	-13.40**	2.18	-18.76	-8.04
PSYS	Baseline	Week 2	-8.10**	1.64	-12.12	-4.08
		End of Treatment	-9.26**	1.90	-13.92	-4.59
CA	Baseline	Week 2	-10.37**	2.79	-17.22	-3.51
		End of Treatment	-15.95**	3.41	-24.33	-7.57
CF	Baseline	Week 2	-9.59**	1.82	-14.06	-5.13
		End of Treatment	-14.21**	2.23	-19.68	-8.73

*$p < .0017$ (corrected error rate, Bonferroni)

**$p < .001$

In order to remove the variance of depressive symptom improvements from CNS-VS neurocognitive domain variables at each time point, each CNS-VS neurocognitive domain was regressed onto the BDI-II score at the same time point (example: baseline NCI score was regressed onto baseline BDI-II score; week two NCI score was regressed onto week two BDI-II

score; end-of-treatment NCI score was regressed onto end-of-treatment BDI-II score). The residual values from these regressions were saved as new variables, as their values represented changes in neurocognitive performance across TMS treatment intervals independent of changes in depressive symptoms. Those new variables were then used as the dependent variables in another series of repeated measures split-plot ANOVAs (time: baseline, two weeks, post-treatment; cognitive function groups: 0 = MCI, 1 = non-MCI) on the new CNS-VS domain variable independent of BDI-II scores. In order to prevent the error rate from being compounded more than necessary, only the CNS-VS neurocognitive domains that displayed significant improvement earlier were included in these analyses: NCI, PROSS, EF, PSYS, CA, and CF.

Type 1 error rate had to be corrected even further for these analyses. The new further-corrected error rate was determined using Bonferroni's alpha correction formula, $\alpha_{PC} = \alpha/C$ (Maxwell & Delaney, 2004, p. 202), where $\alpha = .005$ and $C = 6$. The resulting corrected error per contrast was $\alpha_{PC} = .0008$. If any significant results were found here, post-hoc pairwise Bonferroni comparisons were examined. Type 1 error rate was corrected again using Bonferroni's alpha correction formula, $\alpha_{PC} = \alpha/C$ (Maxwell & Delaney, 2004, p. 202), where $\alpha = .0008$ and $C = 3$. The resulting corrected error per contrast was $\alpha_{PC} = .0003$. For instances in which sphericity could not be assumed, Greenhouse-Geisser's sphericity correction was used, as it is the more conservative correction of sphericity. None of these analyses showed significant results (see Table 5), indicating any potential treatment improvements in neurocognitive functioning as a result of TMS treatment occur as a function of TMS treating depressive symptoms.

Table 5

ANOVAs: TMS on Neurocognitive Performance Independent of Depressive Symptom Changes

		$\hat{\varepsilon}$	*df*	Mean Square	*F*	η_p^2
NCI	TMS Treatment Over Time	.88	1.76	0.01	0.04	.001
	Error	.88	116.33	0.34		
PROSS	TMS Treatment Over Time	-	2	0.01	0.03	<.001
	Error	-	132	0.22		
EF	TMS Treatment Over Time	-	2	0.01	0.02	<.001
	Error	-	132	0.36		
PSYS	TMS Treatment Over Time	.87	1.74	0.004	0.02	<.001
	Error	.87	114.93	0.27		
CA	TMS Treatment Over Time	.88	1.76	0.02	0.04	.001
	Error	.88	116.17	0.44		
CF	TMS Treatment Over Time	-	2	0.01	0.02	<.001
	Error	-	132	0.32		

* $p < .0008$ (corrected error rate, Bonferroni)

Discussion

TMS is a previously established treatment for treatment-resistant, or refractory, depression; however, its efficacy has not been established in treating depression among individuals diagnosed with MCI. Prior research indicates that MCI and depression are not only comorbid, but depression is likely a prodromal factor to the onset of MCI/dementia. While depression and MCI are two separate disorders, research has shown the two disorders to be

strongly linked. The aim of this research study was to determine (1) if TMS can be an efficacious treatment for depression among individuals diagnosed with MCI and (2) if TMS can improve neurocognitive functioning independent of any improvements in depressive symptoms. Based on the current body of research, two hypotheses were generated: (1) TMS will be equally efficacious in treating depressive symptoms for individuals with MCI and individuals without MCI; (2) TMS will create significant improvements among neurocognitive functioning, and these improvements will remain significant independent of depressive symptom improvement.

The results of this study indicate that TMS can be an efficacious treatment for depression among individuals with MCI. Both the MCI group and non-MCI group experienced significant reduction in depressive symptoms across TMS treatment at all three time points. It is also important to note that the two groups did not differ significantly in their treatment progression, indicating that the MCI group experienced depressive symptom reduction at a statistically similar rate to the non-MCI group. As a result, these results allow for a rejection of the null hypothesis, and therefore provide empirical support that TMS may be equally efficacious in treating depression among individuals diagnosed with MCI compared to those of average neurocognitive functioning. While this study appears to be the first empirical examination of comparative efficacy between MCI and non-MCI groups, the results are consistent with hypotheses presented in the literature. Previous research has indicated that TMS can create significant changes in cortical excitability and neuroplasticity among individuals with MCI/dementia (Alberici, et al., 2008; Elder & Taylor, 2014; Issac, Chandra, & Nagaruju, 2013; Luber & Lisanby, 2014; Nardone, et al., 2015; Pennisi, et al., 2006), which provides support for the prediction of TMS as an efficacious treatment method for individuals with MCI. Given the current body of research, in conjunction with the results of this current study, TMS appears to produce changes in cortical

excitability and neuroplasticity, and in turn, significant improvements in depressive symptoms, for individuals with MCI at a statistically similar level to individuals with average neurocognitive functioning. In other words, TMS appears to be equally efficacious in treating depressive symptoms for individuals with lower levels of cognitive function and individuals with average levels of cognitive function.

With regards to the second hypothesis, the results indicated significant improvements in neurocognitive functioning across some CNS-VS domains, but not all. TMS treatment appears to produce significant improvements in gross neurocognition index, processing speed, executive function, psychomotor speed, complex attention, and cognitive flexibility. However, composite memory, verbal memory, visual memory, and reaction time did not improve significantly throughout the duration of TMS treatment. Further analyses revealed that any significant improvements in neurocognitive domains did not remain significant after controlling for the variance of depressive symptom improvement, indicating that while TMS alone may improve neurocognitive functioning, it does so as a function of treating depressive symptoms. As a result, the null hypothesis could not be rejected. At first glance, results appear to contradict results within the current body of literature. Three studies have previously produced results indicating TMS is able to produce improvements in neurocognitive performance (Bentwich, et al., 2011; Lee, et al., 2016; Rabey & Dobrenevsky, 2016). However, it is important to note that each of these studies incorporated a form of cognitive training during the TMS administration procedures. These results in conjunction with the results of the current study appear to indicate that TMS alone may not be efficacious in improving neurocognitive functioning independent of depressive symptoms. Neurocognitive function is often seen as a dimension of depressive disorders – in these instances, TMS is able to treat neurocognitive function; however, TMS in

combination with cognitive training (deemed TMS-Cog; Bentwich, et al., 2011; Lee, et al., 2016; Rabey & Dobrenevsky, 2016) may produce neurocognitive improvements above changes attributed to depressive symptom improvement.

Limitations and Future Considerations

This study, like all studies, is not without its limitations. The largest limitation in this study concerns the sample. Because this study used archival data, i.e. data that had been previously collected, the active researchers here had very little control over sample selection and methodologies implemented. As a result, some potential limitations arose.

Much of the previous research in MCI/dementia focuses on elderly/geriatric populations. Analysis of the demographics statistics, particularly average age of each group (MCI = 47.76; non-MCI = 42.17), likely do not allow the present results to be generalized to elderly/geriatric populations. As a result, these results may not generalize to elderly individuals diagnosed with MCI/dementia not attributable to depressive symptomology. Also, stemming from sample selection, present researchers cannot be sure if participants within the sample may be diagnosed with true MCI or if any neurocognitive impairments are the results of a depressive pseudodementia presentation. If the observed neurocognitive impairments within the MCI group were due to a depressive pseudodementia presentation, then the neurocognitive results of this research study may be better explained. However, because the etymology of neurocognitive impairments in the present sample cannot be determined, this provides a significant limitation of this study.

Another potential limitation relates to this study's inability to differentiate between amnestic MCI and non-amnestic MCI. Much of the MCI research body emphasizes the differentiation between these two sub-categories of MCI because they each may have different

diagnostic implications and potential disease progressions. However, after further classifying the MCI group into amnestic and non-amnestic MCI, the sizes of each group did not meet power criteria and were significantly different from each other (amnestic MCI n = 24; non-amnestic MCI n = 14). As a result, any comparative analyses performed between these two groups would likely not produce reliable results, and therefore were omitted from this study's design.

It should also be noted that this study lacked a sham-TMS or other form of no-treatment control group. While the non-MCI group provided a comparison group for the MCI group in the depressive symptom analyses, this study lacked a no-treatment or treatment-as-usual control group. As a result, this study could not control for potential placebo effects, nor could it provide any statements as to treatment efficacy above other forms of treatment. However, one could extrapolate the presence of a true treatment effect among both the MCI and non-MCI group for TMS treatment, as the effect sizes observed within this study are comparable, if not stronger, than those found in previous studies (Sabesan, et al., 2015). Regardless, the lack of a no-treatment control group within this study should be considered when interpreting these results.

The archival data used for this study also did not include follow-up examination data. As a result, this study lacked follow-up assessment results and therefore cannot make statements regarding the continuation of treatment effects post-treatment. Previous research has shown TMS to produce long-lasting treatment effects even after cessation of treatment (Machado, et al., 2013; Simpson, et al., 2009). In fact, some research indicates that TMS may have long-lasting benefits for up to 84.2% of patients, with effects maintained at 6-month follow-up (treatment benefits defined by the absence of depressive symptom relapse; Janicak, et al., 2010). Therefore, it could be argued that those long-lasting effects likely generalize to this research study; however, the

lack of follow-up measures remains a limiting factor in speaking to the long-term efficacy of TMS treatment for individuals with MCI.

Additionally, the extracted data set used for this study did not contain complete information on participant's racial or ethnic background. Of the 68 total participants data points included in this study, 28 did not report any racial or ethnic background. Of the remaining 48 participants, 47 of whom identified as Caucasian, and one identified as African American. Because of this distribution, this study could not examine potential racial differences in TMS treatment outcomes.

Another potential limitation is the assessment battery used to assess neurocognitive functioning (CNS-VS). While the CNS-VS has shown promising reliability and validity, particularly in its uses for identification of MCI, diagnostic specificity, and its uses for research within a clinical setting (Gualtieri, 2004; Gualtieri & Johnson, 2005; Gualtieri & Johnson, 2006; Gualtieri & Johnson, 2008; Gualtieri, Johnson, & Benedict, 2006), it is possible that a more extensive neurocognitive assessment battery that targets each specific neurocognitive domain (i.e. executive functioning, processing speed, etc.) may provide a more accurate representation of each participant's neurocognitive profile at baseline assessment and also as they progress in TMS treatment.

Also related to assessment, the BDI-II has a number of questions that assess the cognitive symptoms of depression (i.e. "Concentration Difficulty" and "Indecisiveness"). Researchers examining the psychometric properties of the BDI-II have performed factor analyses and identified these cognitive questions to be an independent factor, labeled the "cognitive-affective" factor (Brown, Kaplan, & Jason, 2012; Dozois, Dobson, & Ahnberg, 1998, p. 84). This must be taken into consideration when analyzing the non-significance of the neurocognitive improvement

after controlling for depressive symptom change. Because the variance of depressive symptom severity (as assessed by the BDI-II) was removed from the model, the resulting neurocognitive scores (as assessed by the CNS-VS) also had neurocognitive variance assessed by the BDI-II removed from the model. That being said, it is possible that the results from these particular analyses underestimate the effects of neurocognitive improvement as a result of TMS treatment over time independent of depressive symptom improvement. While the cognitive-affective factor of the BDI-II could have been removed separately from the BDI-II total scores before covarying depressive symptoms from the neurocognition indices, doing so would likely decrease the overall reliability and validity of the BDI-II total scores, thus introducing further error into the overall model (Brown, et al., 2012; Dozois, et al., 1998; Storch, Roberti, & Roth, 2004).

A final limitation within this study regards the positioning of the TMS coil during TMS treatment. The EVMS TMS Treatment Program uses the Pascual-Leone method of coil placement in which the TMS coil is placed 5cm rostrally from the MT area of the primary motor cortex to identify the DLPFC, and 2cm rostrally to identify the SMA. While the Pascual-Leone method of coil placement is commonly used, both in the clinical and research settings, some neuronavigation studies have shown that fMRI-guided TMS coil placement may yield the strongest behavioral effects in comparison to EEG-guided approach and the Pascual-Leone method of coil placement (Sack, et al., 2009). Based on this information, using the Pascual-Leone method of coil placement may have been a potential contributing factor into the lack of treatment improvements in neurocognitive performance independent of depressive symptom improvement.

The previously mentioned limitations warrant careful analysis of the findings and interpretations of this study, specifically the neurocognitive performance results. Many of these

limiting factors could provide potential explanations as to why neurocognitive improvements were not found to remain significant after controlling for depressive symptom improvements. Also, while the depressive symptom improvement results are tantalizing, long-term maintenance of treatment gains for individuals with MCI is not known. As a result, future research into this area should attempt to rectify some of these limitations in order to improve the generalizability and overall impact of results. The optimal research method that could address many of these limitations would be a randomized clinical trial (RCT) which includes a sham-TMS control condition.

Conclusions

The present study is among the first empirical studies to actively examine the treatment efficacy for TMS in treating depression among individuals with impaired cognitive functioning. Additionally, this study is among the first to provide empirical support for the comparative efficacy of TMS by comparing treatment outcomes among individuals with MCI to treatment outcomes among individuals with average neurocognitive functioning. Overall, this study provides support for the statement that TMS may be an efficacious treatment method for treating treatment-resistant, or refractory, depression among individuals diagnosed with MCI. The results of this study also demonstrate that TMS alone may not be sufficient in treating cognitive impairments among individuals with MCI, and treatment protocols with this desired outcome should incorporate some form of cognitive training, as suggested by the literature.

This study also provides further support to the interconnectedness of depressive disorders and cognitive impairment and the presence of depressive pseudodementia. The results showed significant improvements among multiple neurocognitive domains, but these improvements appeared to occur as a function of improving depressive symptoms, indicating that these

cognitive impairments were likely caused by the depressive symptoms. In turn, it becomes increasingly clear that depression and MCI can be significantly connected, and therefore accurate differential diagnosis between these two disorders is paramount.

Further research is still needed in generating an empirical body of support for the efficacy of TMS in treating depression among individuals diagnosed with MCI. While this study produced promising results, hopefully it will encourage future researchers to examine this topic even further to determine whether or not TMS may provide an efficacious and effective method of treating depression for this population.

REFERENCES

Alberici, A., Bonato, C., Calabria, M., Agosti, C., Zanetti, O., Miniussi, C., Padovani, A., Rossini, P., & Borroni, B. (2008). The contribution of TMS to frontotemporal dementia variants. *Acta Neurol Scand, 118,* 275-280. doi:10.1111/j.1600-0404.2008.01017.x

Alexopolous, G., & Kelly, R. (2009). Research advances in geriatric depression. *World Psychiatry, 2009,* 140-149. doi:10.1002/j.2051-5545.2009.tb00234.x.

Alloy, L., LaBelle, D., Boland, E., Goldstein, K., Jenkins, A., Shapero, B., Black, S., & Obraztsova, O. (2016). Depressive and Bipolar Disorders. In J. Maddux and B. Winstead (Eds.), *Psychopathology foundations for a contemporary understanding* (pp.182-217). New York, NY: Routledge.

Alzheimer's Association. (2016). 2016 Alzheimer's disease facts and figures. *Alzheimer's and Dementia, 12*(4). Retrieved from http://www.alz.org/documents_custom/2016-facts-and-figures.pdf

American Psychiatric Association. (1978). *Electroconvulsive Therapy, Task Force Report* (Report No. 14). Washington, D.C.: American Psychiatric Association.

Arns, M., Drinkenburg, W., Fitzgerald., P., & Kenemans, L. (2012). Neurophysiological predictors of non-response to rTMS in depression. *Brain Stimulation, 2012,* 1-8. doi:10.1016/j.brs.2011.12.003

Beck, A., Epstein, N., Brown, G., & Steer, R. (1988). An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting and Clinical Psychology, 56,* 893-897. doi:10.1037/0022-006X.56.6.893

Bentwich, J., Dobronevsky, E., Aichenbaum, S., Shorer, R., Peretz, R., Khaigrekht, M., Marton, R., & Rabey, J. (2011). Beneficial effect of repetitive transcranial magnetic stimulatioin

combined with cognitive training for the treatment of Alzheimer's disease: a proof of concept study. *Journal of Neural Transmission, 118*, 463-471. doi:10.1007/s00702-010-0578-1.

Bieniek, K., Blitterswijk, M., Baker, M., Petrucelli, L., Rademakers, R., & Dickson, D. (2014). Expanded C90RF72 hexanucleotide repeat in depressive pseudodementia. *Journal of the American Medical Association Neurology, 71*, 778-781. doi:10.1001/jamaneurol.2013.6368.

Brown, M., Kaplan, C., & Jason, L. (2012). Factor analysis of the Beck Depression Inventory II with patients with chronic fatigue syndrome. *Journal of Health Psychology, 17*, 199-808. doi: 10.1177/1359105311424470.

Byers, A. & Yaffe, K. (2011). Depression and risk of developing dementia. *Nature Reviews Neurology, 7*, 323-331. doi:10.1038/nrmeurol.2011.60.

Castilla-Puentes, R. & Habeych, M. (2010). Subtypes of depression among patients with Alzheimer's disease and other dementias. *Alzheimer's and Dementia, 6*, 63-69. doi:10.1016/j.jalz.2009.04.1232.

Chappell, A., (2016). *Cognitive performance as a function of right-sided, low-frequency rTMS administration using CNS Vital Signs* (Unpublished doctoral dissertation). Virginia Consortium Program in Clinical Psychology, Norfolk, VA.

CNS Vital Signs, LLC. (2003). *CNS vital signs interpretation guide*. Morrisville, NC: CNS Vital Signs, LLC.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.), Hillsdale, NJ: Erlbaum.

Cona, G., Marino, G., & Semenza, C. (2017). TMS of supplementary motor area (SMA) facilitates mental rotation performance: evidence for sequence processing in SMA. *NeuroImage, 146*, 770-777. doi:10.1016/j.neuroimage.2016.10.032.

Cotelli, M., Manenti, R., Cappa, S., Geroldi, C., Zanetti, O., Rossini, P., & Miniussi, C. (2006). Effect of transcranial magnetic stimulation on action naming in patients with Alzheimer Disease. *Archives of Neurology, 63*, 1602-1604. doi:10.1001/archneur.63.11.1602.

Cowey, A. (2005). The Ferrier Lecture 2004: what can transcranial magnetic stimulation tell us about how the brain works? *Philosophical Transactions of the Royal Society, 360*, 1185-1205. doi:10.1098/rstb.2005.1685

Cusin, C., Yang, H., Yeung, A., & Fava, M. (2009). Chapter 2: Rating Scales for Depression. Baer, L., Blais, M. (eds). *Handbook of Clinical Rating Scales and Assessments in Psychiatry and Mental Health.* (pp. 7-35). doi:10.1007/978-1-59745-387-5_2.

Dozois, D., Dobson, K., & Ahnberg, J. (1998). A psychometric evaluation of the Beck Depression Inventory-II. *Psychological Assessment, 10*(2), 83-89.

Dybedal, G., Tanum, L. Sundet, K., Bjøoseth, T. (2015). The role of baseline cognitive functions in the neurocgotnive effects of electroconvulsive therapy in depressed elderly patients. *Clinical Neuropsychologist, 29*, 487-508. doi:10.1080/13854046.2015.1050457.

Elder, G. & Taylor, J. (2014). Transcranial magnetic stimulation and transcranial direct current stimulation: treatments for cognitive and neuropsychiatric symptoms in the neurodegenerative dementias? *Alzheimer's Research and Therapy, 6*(74), 1-11. doi:10.1186/s13195-014-0074-1.

Enache, D., Winblad, B., & Aarsland, D. (2011). Depression in dementia: epidemiology, mechanisms, and treatment. *Current Opinion in Psychiatry, 24*, 461-472. doi:10.1097/YCO.0b013e32834bb9d4.

Farias, S., Mungas, D., Reed, B., Harvey, D., & DeCarli, C. (2009). Progression of mild cognitive impairment to dementia in clinical vs community-based cohorts. *Archives of Neurology, 66*, 1151-1157. doi:10.1001/archneurol.2009.106.

Farina, N., Morrell, L., & Banarjee, S. (2016). What is the therapeutic value of antidepressants in dementia? A narrative review. *International Journal of Geriatric Psychiatry, 2016*, 1-18. doi:10.1002/qps.4566.

Fontenelle, L., Nascimento, A., Mendlowicz, M., Schavitt, R., & Versiani, M. (2007). An update on pharmacological treatment of obsessive-compulsive disorder. *Expert Opinion on Pharmacotherapy, 8*(5), 1-21.

Gilmartin, J., Väämäinen, S., Törmälehto, S., Bell, J., Lönnroos, E., Salo, L., Hallikainen, I., Martikainen, J., & Koivisto, A. (2015). Depressive symptoms are associated with analgesic use in people with Alzheimer's disease: Kuopio ALSOVA study. *Public Library of Science, 10*(2), 1-18. doi:10.1371/journal.pone.0117926.

Grant, M. (n.d.). Beck Anxiety Inventory. Myrtle Beach, SC: Coastal Cognitive. Retrieved from www.coastalcognitive.com

Gualtieri, C. (2004). Dementia screening using computerized tests. *Journal of Insurance Medicine, 36*, 213-227. Retrieved from ncneuropsych.com.

Gualtieri, C. & Johnson, L. (2005). Neurocognitive testing supports a broader concept of mild cognitive impairment. *American Journal of Alzheimer's Disease and Other Dementias, 20*, 359-366. doi:10.1177/153331750502000607.

Gualtieri, C. & Johnson, L. (2006). Reliability and validity of a computerized neurocognitive test battery, CNS vital signs. *Archives of Clinical Neuropsychology, 21*, 623-643. doi:10.1016/j.acn.2006.05.007.

Gualtieri, C. & Johnson, L. (2008). Age-related cognitive decline in patients with mood disorders. *Progress In Neuro-Psychopharmacology and Biological Psychiatry, 32*, 962-967. doi:10.1016/j.pnphp.2007.12.030.

Gualtieri, C. T., Johnson, L. G., & Benedict, K. B. (2006). Neurocognition in depression: patients on and off medication versus healthy comparison subjects. *Journal of Neuropsychiatry and Clinical Neuroscience, 18*, 217-225.

Han, L., McCusker, J., Cole, M., Abrahamowicz, Michal, & Capek, Radan. (2008). 12-month cognitive outcomes of major and minor depression in older medical patients. *The American Journal of Geriatric Psychiatry, 16*, 742-751. doi:10.1097/JGP.0b013e31817c6ad7.

Hancock, P., & Larner, A. (2015). Cornell scale for depression in dementia: clinical utility in a memory clinic. *International Journal of Psychiatry in Clinical Practice, 19*, 71-74. doi:10.3109/13651501.2014.940056.

Harvey, P. (2012). Clinical applications of neuropsychological assessment. *Dialogues in Clinical Neuroscience, 14*, 91-99.

Herbsman, T., Avery, D., Ramsey, D., Holtzheimer, P., Wadjik, C., Hardaway, F., Haynor, D., George, M., & Nahas, Z. (2009). *Journal of Biological Psychiatry, 66*, 509-515. doi:10.1016/j.biopsych.2009.04.034

Hesser, K., Bleckwenn, M., Weise, B., Mamone, S., Riedel-Heller, S., Stein, J., Lümann, D., Posselt, T., Fuchs, A., Pentzek, M., Weyerer, S., Werle, J., Weeg, D., Bickel, H.,

Brettschneider, C., König, H., Maier, W., Scherer, M., & Wagner, M. (2016). Late-life depressive symptoms and lifetime history of major depression: cognitive deficits are largely due to incipient dementia rather than depression. *Journal of Alzheimers Disease, 54*, 185-199. doi:10.3233/JAD-1602209.

Horvath, J., Perez, J., Farrow, L., Fregni, F., & Pascual-Leone, A. (2011). Transcranial magnetic stimulation: a historical evaluation and future prognosis of therapeutically relevant ethical concerns. *Journal of Medical Ethics, 37*, 137-143. doi:10.1136/jme.2010.039966.

Hyer, L., Sohnle, S., Ashraf, A., Hamer, R., & Ragan, A. (2003). Use of the binary Beck Depression Inventory in nursing homes. *Clinical Gerontologist, 26*, 13-28. doi:10.1300/J018v26n03_03.

Issac, T., Chandra, S., & Nagaraju, B. (2013). Transcranial magnetic stimulation in patients with early cortical dementia: a pilot study. *Annals of Indian Academy of Neurology, 16*, 619-622. doi:10.4103/0972-2327.120493.

Jamaluddin, F., Abdullah, S., & Yahaya, S. (2014). Winsorization approach in testing the equality of independent groups. *AIP Conference Proceedings, 1605*, 1061-1066. doi: 10.1063/1.4887738.

Janicak, P. & Dokucu, M. (2015). Transcranial magnetic stimulation for the treatment of major depression. *Neuropsychiatric Disease and Treatment, 11*, 1549-1560. doi:10.2147/NDT.S67477.

Janicak, P., et al. (2010). Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during 6-month, multisite, open-label study. *Brain Stimulation, 3*, 187-199. doi:10.1016/j.brs.2010.07.003.

Jorge, R., Moser, D., Acion, L., & Robinson, R. (2008). Treatment of vascular depression using repetitive transcranial magnetic stimulation. *Archives of General Psychiatry, 65*, 268-276.

Kelly, B. & Peterson, R. (2007). Alzheimer's disease and mild cognitive impairment. *Neurologic Clinics, 25*, 577-609.

Kendler, K., Thornton, L., & Gardner, C. (200). Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. *American Journal of Psychiatry, 157*, 1243-1251. doi:10.1176/appi.ajp.157.8.1234

Kitching, D. (2015). Depression in dementia. *Australian Prescriber, 38*, 209-211. Retrieved from www.australianprescriber.com.

Knapskog, A., Barca, M., & Engedal, K. (2014). Prevalence of depression among memory clinic patients as measured by the Cornell Scale of Depression in Dementia. *Aging and Mental Health, 18*, 579-587.

Kolshus, E., Jelovac, A., & McLaughlin, D. (2016). Bitemporal v. high-dose right unilateral electroconvulsive therapy for depression: a systematic review and meta-analysis of randomized controlled trials. *Psychological Medicine 47*, 518-530. doi:10.1017/S0033291716002737.

Lannone, A., Cruz, A., Brasil-Neto, J., & Barros, R. (2016). Transcranial magnetic stimulation and transcranial direct current stimulation appear to be safe neuromodulatory techniques useful in the treatment of anxiety disorders and other neuropsychiatric disorders. *Arquivos de Neuro-Psiquiatria, 74*, 829-835. doi:10.1590/0004-282X201600115.

Lee, J., Choi, B., Oh, E., Sohn, E., & Lee, A. (2016). Treatment of Alzheimer's disease with repetitive transcranial magnetic stimulation combined with cognitive training: a

prospective, randomized, double-blind, placebo-controlled study. *Journal of Clinical Neurology, 12*, 57-64. doi:10.3988/jcn.2016.12.1.57.

Li, R. & Singh, M. (2014). Sex differences in cognitive impairment and Alzheimer's disease. *Front Neuroendocrinology, 35*, 385-403.doi:10.1016/j.yfrne.2014.01.002.

Luber, B., Davis, S., Bernhardt, E., Neacsiu, A., Kwapil, L., Lisanby, H., & Strauman, T. (2017). Using neuroimaging to individualize TMS treatment for depression: toward a new paradigm for imaging-guided intervention. *NeuroImage, 148*, 1-7. doi:10.1016/j.neuroimage.2016.12.083.

Luber, B. & Lisanby, S. (2014). Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). *Neuroimage, 85*, 961-970. doi:10.1016/j.neuroimage.2013.06.007.

Machado, S., Arias-Carrion, O., Paes, F., Viera, R., Caixeta, L., Novaes, F., Marinho, T., Almada, L., Silva, A., & Nardi, A. (2013). Repetitive transcranial magnetic stimulation for clinical applications in neurological and psychiatric disorders: an overview. *The Eurasian Journal of Medicine, 45*, 191-206. doi:10.5152/eajm.2013.39.

Magnezi, R., Aminov, E., Shmuel, D., Dreifuss, M., & Dannon, P. (2016). Comparison between neurostimulation techniques repetitive transcranial magnetic stimulation vs electroconvulsive therapy for the treatment of resistant depression: patient preference and cost-effectiveness. *Patient Preference and Adherence, 10*, 1481-1487. doi:10.2147/PPA.S105654.

Mantovani, A. (n.d.). The application of transcranial magnetic stimulation (TMS) to the treatment of anxiety disorders. [PowerPoint]. Retrieved from Columbia University

Department of Psychiatry – Brain Stimulation and Therapeutic Modulation http://www.brainstimulation.columbia.edu/

Mantovani, A., Simpson, H., Fallon, B., Rossi, S., & Lisanby, S. (2010). Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. *International Journal of Neuropsychopharmacology*, *13*, 217-227. doi:10.1017/S1461145709990435.

Maxwell, S. & Delaney, H. (2004). *Designing Experiments and Analyzing Data: A Model Comparison Perspective, Second Edition*. New York, NY: Taylor & Francis Group, LLC.

McDonald, W. (2016). Neuromodulation treatments for geriatric mood and cognitive disorders. *American Journal of Geriatric Psychology, 24,* 1130-1141. doi:10.1016/j.jaqp.2016.08.014.

Mirza, S., Wolters, F., Swanson, S., Koudstaal, P., Hofman, A., Tiemeier, H., & Ikram, M. (2016). 10-year trajectories of depressive symptoms and risk of dementia: a population-based study. *Lancet Psychiatry, 3,* 628-635. doi:10.1016/S2215-0366(16)00097-3.

Mitchell, A. & Shiri-Freshki, M. (2009). Rate of progression of mild cognitive impairment to dementia – meta-analysis of 41 robust inception cohort studies. *Acta Psychiatrica Scandinavia, 119,* 252-265. doi:10.1111/j.1600-0447.2008.01326.x.

Moyle, Hsu, Lieff, & Vernooij-Dassen. (2010). Recommendations for staff education and training for older people with mental illness in long-term aged care. *International Psychogeriatrics, 22,* 1097-1106. doi:10.1017S/1041610210001754.

Nardone, R., Tezzon, F., Höller, Y., Golaszewski, S., Trinka, E., & Bringo, F. (2014). Transcranial magnetic stimulation (TMS)/repetitive TMS in mild cognitive impairment

and Alzheimer's disease. *Acta Neurologica Scandinavia, 129*, 351-366. doi:10.1111/ane.12223.

National Institute on Aging. (2015). *2014-2015 Alzheimer's disease progress report: advancing research toward a cure*. Retrieved from https://www.nia.nih.gov/alzheimers/publication/2014-2015-alzheimers-disease-progress-report/introduction

Pascual-Leone, A., Tarazona, F., Keenan, J., Tormos, J., Hamilton, R., & Catala, M. (1999). Transcranial magnetic stimulation and neuroplasticity. *Neuropsychologia, 37*, 207-217.

Paula, J., Miranda, D., Nicolato, R., Moraes, E., Bicalho, M., & Malloy-Diniz, L. (2013). Verbal learning on depressive pseudodementia: accentuate impairment of free recall, moderate on learning processes, and spared short-term and recognition memory. *Arquivos de Neuro-Psiquiatria, 71*, 596-599. doi:10.1590/004-282X20130102.

Pennisi, M., Lanza, G., Cantone, M., Ricceri, R., Spampinato, C., Pennisi, G, Lazzaro, V., & Bella, R. (2016). Correlation between motor cortex excitability changes and cognitive impairment in vascular depression: pathophysiological insights from a longitudinal TMS study. *Hindawi Publishing Corporation, 2016,* 1-10. doi:10.1155/2016/8154969.

Perera, T., George, M., Grammer, G., Janicak, P., Pascual-Leone, A., & Wirecki, T. (2016). The clinical TMS society consensus review and treatment recommendations for TMS therapy for major depressive disorder. *Brain Stimulation, 9,* 336-346. doi:10.1016/j.brs.2016.03.010.

Peterson, R. (2013). Countdown to 2025: progress on ending Alzheimer's disease. [PowerPoint]. Retrieved from www.mind.uci.edu/wp-content/uploads/.../Ronald-Petersen-DSM-5.pdf

Peterson, R. (2007). Clinical diagnosis of mild cognitive impairment. [PowerPoint]. Retrieved from https://www.alz.washington.edu/NONMEMBER/SPR07/ronpete.pdf

Pine, D., Cohen, E., Cohen, P., & Brook, J. (1999). Adolescent depressive symptoms as predictors of adult depression: moodiness or mood disorder? *American Journal of Psychiatry, 156*, 133-135. doi:10.1176/ajp.156.1.133.

Potes, A., Gagnon, G., Touré, E., & Perreault, M. (2016). Patient and clinician assessments of symptomatology changes on older adults following a psycho-educational program for depression and anxiety. *Psychiatric Quarterly, 2016*, 649-662. doi:10.1007/s11126-016-9416-4.

Rabey, J. & Dobrenevsky, E. (2016). Repetitive transcranial magnetic stimulation (rTMS) combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease: clinical experience. *Journal of Neural Transmission, 123*, 1449-1455. doi:10.1007/s00702-016-1606-6.

Ricardo-Garcell, J., González-Olvera, J., Miranda, E., Harmony, T., Reyes, E., Almeida, L., Galán, L., Díaz, D., Ramírez, L., Fernández-Bouzas, A., & Aubert, E. (2009). EEG sources in a group of patients with major depressive disorder. *International Journal of Psychophysiology, 71*, 70-74. doi:10.1016/j.ijpsycho.2008.07.021.

Sabesan, P., Lankappa, S., Khalifa, N., Krishnan, V., Gandhi, R., & Palanyappan, L. (2015) Transcranial magnetic stimulation for geriatric depression: promises and pitfalls. *World Journal of Psychiatry, 5*, 170-181. doi:10.5498/wjp.v5.i2.170.

Sack, A., Kodosh, R., Schuhmann, T., Moerel, M., Walsh, V., & Goebel, R. (2009). Optimizing functional accuracy of TMS in cognitive studies: a comparison of methods. *Journal of Cognitive Neuroscience, 21*, 207-221. doi:10.1162/jocn.2009.21126.

Saykin, A. & Rabin, L. (2014). Dementias and Neurodegenerative Diseases. In M. W. Parsons and T. A. Hammeke (Eds.), *Clinical neuropsychology: a pocket handbook for assessment* (237-265). Washington, DC: American Psychological Association.

Schoenberg, M. (n.d.). Age associated cognitive deceline and mild cognitive impairment (MCI). [PowerPoint]. Retrieved from www.thecjc.org/pdf/gc09/gc09-2.pdf

Schroevers, M., Tovote, K., Snippe, E., & Fleer, J. (2016). Group and individual mindfulness-based cognitive therapy (MBCT) are both effective: a pilot randomized controlled trial in depressed people with a somatic disease. *Mindfulness, 7*, 1139-1346. doi:10.1007/s12671-016-0575-z.

Segal, D., Coolidge, F., Cahill, B., & O'Riley, A. (2008). Psychometric properties of the Beck Depression Inventory-II (BDI-II) among community-dwelling older adults. *Behavioral Modification, 23*, 3-20. doi:10.1177/0145445507303833.

Segal, Z., Kennedy, S. Gemar, M., Hood, K., Pedersen, R., & Buis, T. (2006). Cognitive reactivity to sad mood provocation and the prediction of depressive relapse. *Archives of General Psychiatry, 6*, 749-755. doi:10.1001/archipsyc.63.7.749

Seidel, S., Dal-Bianco, P., Pablik, E., Müller, N., Schadenhofer, C., Lamm, C., Klösch, G., Moser, D., Klug, S., Pusswald, G., Auff, E., & Lehrner, J. (2015). Depressive symptoms are the main predictor for subjective sleep quality in patients with mild cognitive impairment – a controlled study. *Public Library of Science*, *10*(6), 1-14. doi:10.1371/journal.pone,0128139.

Sheskin, D. (2011). *Handbook of Parametric and Nonparametric Statistical Procedures, Fifth Edition*. Boca Raton, FL: Chapman and Hall CRC.

Simpson, K., Welch, M., Kozel, F., Demitrack, M., & Nahas, Z. (2009). Cost effectiveness of transcranial magnetic stimulation in the treatment of major depression: a health economics analysis. *Advances in Therapy, 26,* 346-368. doi:10.1007/s12325-009-0013-x.

Sinanović, O., Hudić, J., Zukić, S., Kapidžić, A., Zonić, L., & Vidović, M. (2015). Depression and dementia in Parkinson's disease. *Acta Clinica Croatica, 54,* 73-76. Retrieved from http://hrcak.srce.hr/acta-clinica-croatica

Storch, E., Roberti, J., & Roth, D. (2004). Factor structure, concurrent validity, and internal consistency of the Beck Depression Inventory – Second Edition in a sample of college students. *Depression and Anxiety, 19,* 187-189.

Story, T., Potter, G., Attix, D., Welsh-Bohmer, K., & Steffens, D. (2008). Neurocognitive correlates of response to treatment in late-life depression. *The American Journal of Geriatric Psychiatry, 16,* 752-759. doi:10.1097/JGP.0b013e31817e739a.

Teng, S., Guo, Z., Peng, H., Xing, G., Chen, H., He, B., McClure, M., & Mu, Q. (2017). High-frequency repetitive transcranial magnetic stimulation over the left DLPFC for major depression: session-dependent efficacy: a meta-analysis. *European Psychiatry, 41,* 75-84. doi:10.1016/j.eurpsy.2016.11.002.

Thomas, A., & Bennett, S. (2014). Depression and dementia: cause, consequence, or coincidence? *Maturitas, 79,* 184-190. doi:10.1016/j.maturitas.2014.05.009.

U.S. Department of Health and Human Services, Food and Drug Administration, & Center for Devices and Radiological Health. (2011). Guidance for industry and Food and Drug Administration staff – class II special controls guidance document: repetitive transcranial magnetic stimulation (rTMS) systems. *Center for Devices and Radiological Health.* Retrieved from http://www.fda.gov/RegulatoryInformation/Guidances/ucm265269.htm

Wild, K., Howieson, D., Webbe, F., Seelye, A., & Kaye, J. (2008). Status of computerized cognitive testing in aging: a systematic review. *Alzheimer's and Dementia, 4*, 428-437. doi:10.1016/j.jalz.2008.07.003.

World Health Organization. (2015). *The epidemiology and impact of dementia: current state and future trends* (WHO Report No. 15.3). Retrieved from http://www.who.int/mental_health/neurology/dementia/en/

APPENDIX A

EVMS TMS REGISTRY CONSENT FORM

DATE: OCTOBER 4, 2012 VERSION 5

Registry Consent Form
Eastern Virginia Medical School (EVMS) Institutional Review Board

Study Title:	Transcranial Magnetic Stimulation (TMS) in Treating Psychiatric Disorders
Name of Investigator:	Serina Neumann, Ph.D.
Sponsor:	Eastern Virginia Medical School
Name of Subject:	

You are being asked to participate in a registry research study involving the collection of information to be entered and used in a patient registry because you received TMS treatment. Information concerning your TMS treatment at Eastern Virginia Medical School will be included in the TMS Patient Registry. Only the investigator(s) of this study will have this information.

The purpose of the databank is to monitor and evaluate factors that may optimize or possibly hinder the effectiveness of TMS treatment of cognitive, behavioral, and emotional disorders (e.g., Major Depressive Disorder, Obsessive Compulsive Disorder, and Post Traumatic Stress Disorder) in humans. Information sent to the TMS Patient Registry includes:

- 1) Neurostar Output- Information regarding your TMS treatment will be included in the databank including: strength, frequency, and duration of magnetic pulses used for TMS treatment.
- 2) CNS Vital Signs Neurocognitive Tests- You will complete computer-based neurocognitive assessments as part of your initial clinical evaluation, after 2 weeks of treatment and at the end of treatment. The assessment battery will include tests examining memory, motor control and speed, attention, reaction time, and planning and organizing information.
- 3) Biological Measures- You will undergo heart rate variability (HRV) and respiration rate measures prior to beginning treatment, after 2 weeks of treatment, and at the end of treatment. This will consist of sitting quietly for 6 minutes while a transmitter electrode, similar to an ECG, placed around your torso measures the intervals between your heart beats. Respiration rate will be measured by visually counting the number of breaths per minute. You will also be asked to take blood tests prior to beginning treatment and at the end of treatment (5 milliliters total per time point). The blood tests will evaluate how TMS affects blood sugar levels and thyroid functioning. A brain activity measure will also be conducted with electroencephalography (EEG) to assess changes throughout the course of treatment at the following time points: prior to beginning treatment, at session 5, session 15, and at the end of treatment.
- 4) Psychological Assessments- You will complete multiple questionnaires evaluating mood, behavior, and sleep quality.
- 5) Medical Chart Information- Information will be obtained from your initial clinical evaluation within your medical chart. All the information is regularly obtained during standard clinical evaluations. Information includes: psychiatric diagnosis, medications, demographic information (e.g., age, DOB, sex, marital status, ethnicity), and alcohol and substance use (e.g., number of drinks of alcohol per week, current substance abuse issues).

The contents of the databank may help us to understand better TMS treatment in humans for various cognitive, behavioral, and emotional disorders. In addition, a part of helping us better understand TMS treatment is to also use the contents of the databank in future studies.

There is no time limit to this databank. Your information will be obtained at the time of your TMS treatment but will be continuously used for the TMS patient registry.

A risk associated with allowing your data to be saved is the release of personal information from your patient record. We will strive to protect your records so that your personal information (like name, address, social security number and phone number) will remain private. There also may be other risks that are unknown and we cannot predict.

You will not be reimbursed for your participation. There are no additional costs to you associated with taking part in this databank.

Although the results of this research may not benefit you directly, they may be made available upon request.

The protected health information (PHI) collected for the purpose of establishing a TMS patient registry will not be shared with any organization other than the investigators at Eastern Virginia Medical School.

All protected health information will be maintained in strict confidence as required by law. However, your protected health information may be disclosed if required by law. Once your protected health information is disclosed for research, such as to the sponsor, federal privacy laws may no longer protect the information.

- You also have the right to review your research records, or someone you designate may review your research records on your behalf, once the study has ended unless prohibited by law.
- Any research information in your medical record will become a permanent part of that document.

Your study records may be reviewed and/or copied in order to meet state and/or federal regulations. Reviewers may include, for example, the Eastern Virginia Medical School Institutional Review Board.

Information learned from this research may be used in reports, presentations and publications. None of these will personally identify you.

Taking part in this TMS patient registry is your choice. If you decide not to take part, your choice will not affect any medical benefits to which you are entitled. You may choose to stop participating at any time.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

In the event of injury resulting from this research study, Eastern Virginia Medical School (EVMS) provides no financial compensation plan or free medical care. If you have any questions pertaining to this research you may contact Dr. Serina Neumann or Dr. Paul Sayegh at 757-446-5888. If you believe you have suffered an injury as a result of your participation in this study, you should contact the principal investigator, Dr. Serina Neumann at 757-446-5888. You may also contact Betsy Conner, Director, EVMS Human Subjects' Protection Program & IRB office, (757) 446-5854. If you have any questions pertaining to your rights as a research subject, you may contact a member of the Institutional Review Board through the Institutional Review Board office at (757) 446-8423.

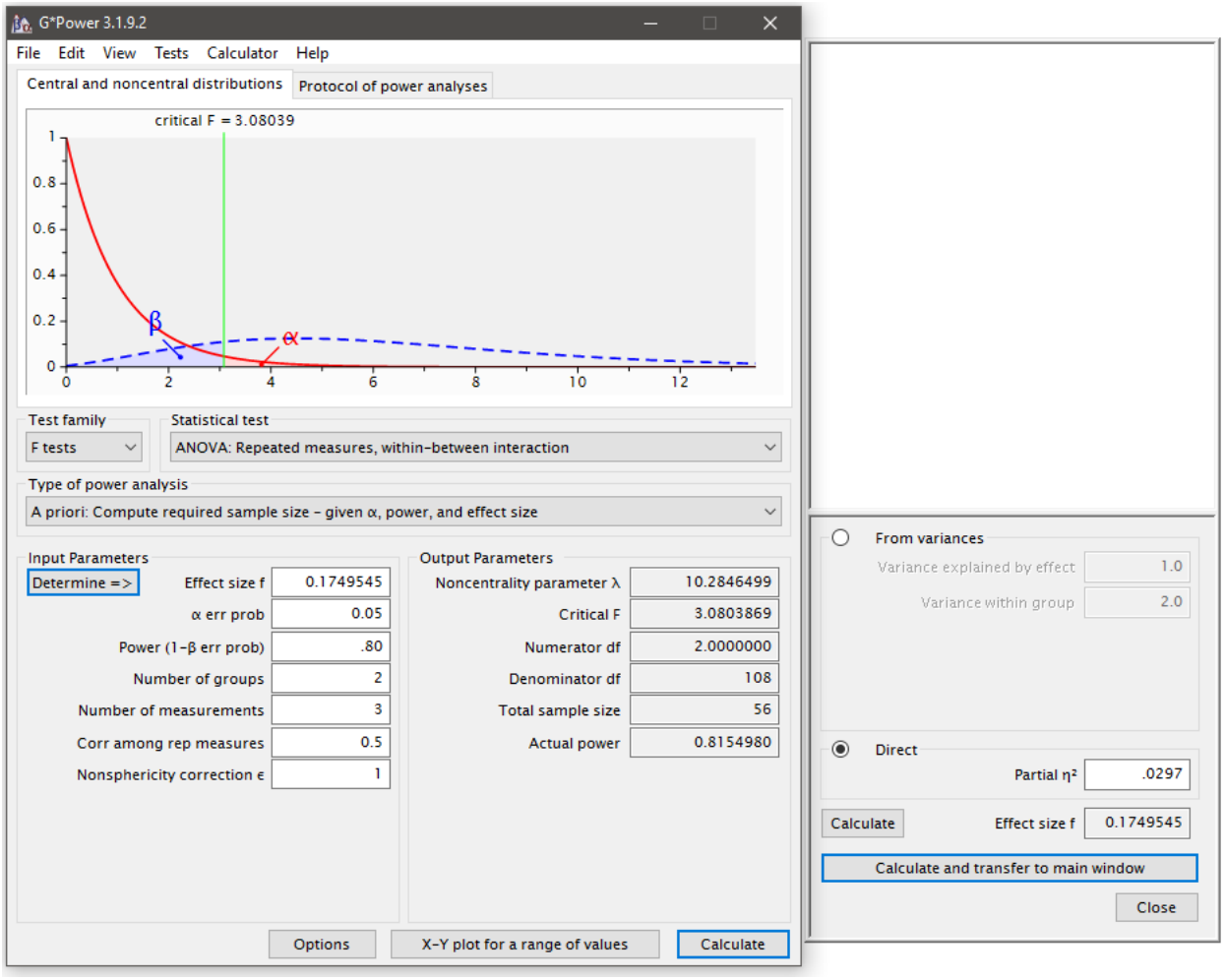
SIGNATURE			
You will get a copy of this signed form. You may also request information from the investigator. By signing your name on the line below, you agree to take part in this study and accept the risks			
_____ Signature of Participant/LAR	_____ Typed or Printed Name	_____ Relationship to Subject	___/___/___ MM/ DD/ YY

STATEMENT OF THE INVESTIGATOR OR APPROVED DESIGNEE	
I certify that I have explained to the above individual the nature and purpose of the study, potential benefits, and possible risks associated with participation in this study. I have answered any questions that have been raised and have witnessed the above signature. I have explained the above to the volunteer on the date stated on this consent form.	
_____ Signature of Investigator or Approved Designee	___/___/___ MM/ DD/ YY

IRB APPROVAL
DATE 12.20.16
EXPIRES
DATE 12.19.17
IRB # 16.07.FB.0135

APPENDIX B

POWER ANALYSIS



Cohen's d = .35 (Sabesan, et al., 2015) was converted to η_p^2 = .030 with the following formula, as found in Cohen (1988, p. 281-285): $f = d/2$; $\eta_p^2 = f^2/(1+f^2)$.

VITA

NAME: Daniel Robert Schaffer

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Daniel Schaffer obtained his Bachelor of Science Degree in Psychology from Barton College in 2014, graduating with honors recognized by the Barton College Honors Program, Alpha Chi Undergraduate National Honor Society, and Magna Cum Laude. While working towards his undergraduate degree, he conducted independent research projects which he presented at the Barton College Scholars Symposium (2013 and 2014) and at the Carolinas Psychology Conference (2014).

After graduating from Barton College, he worked as the Director of Neuromarketing and Neuroscience Research at Howard, Merrell, & Partners, and as a Behavioral Programming Specialist at Longleaf Neuromedical Treatment Center.

Daniel is currently enrolled in graduate school at the Virginia Consortium Program for Clinical Psychology striving towards his Master's Degree in Experimental Psychology and Ph.D. in Clinical Psychology. During his enrolment, he has worked in a variety of clinical settings, including Norfolk General Hospital, Eastern Virginia Medical School, Virginia Beach Public School System, and the Hampton Veterans Administration Medical Center. He has also participated in various research projects, and has presented research for the Society of Behavioral Medicine (2018).