THE EFFECTS OF INTERMITTENT THETA BURST STIMULATION ON WORKING MEMORY IN PATIENTS WITH MAJOR DEPRESSION

by

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Abstract

Background: People with depression struggle with cognitive impairments such as decreased working memory. The brain areas associated with working memory, such as the prefrontal cortex and hippocampus are negatively affected by depression; studies have shown decreased volume, activity, and disturbed brain connectivity. Currently, there is a lack of treatment options for improving working memory in depressed patients. Therefore, the therapeutic potential of intermittent theta-burst stimulation (iTBS) on working memory was explored. iTBS has been shown to be effective in treating mood, increasing plasticity and inducing neurogenesis. These findings suggest a potential for iTBS as a treatment tool for working memory.

Objective: The objective of the present study was to determine whether iTBS treatment is associated with improvement in working memory, and connectivity changes between areas in the prefrontal cortex, hippocampus and the rest of the brain.

Methods: We recruited 10 patients with major depressive disorder (MDD). Patients received the standard 25 days of iTBS treatment. We used the n-back (2-back) task to test working memory during functional magnetic resonance imaging (fMRI) scan. Participants received a fMRI scan before and after the final iTBS treatment. Participants also completed clinical measures (i.e., depression scales) before and after their treatments.

Results: The participants did not show significant improvements in mood and the n-back task (accuracy and reaction time) after the iTBS treatments. There were significant changes in functional connectivity during the resting state scans and for the 0 and 2 back conditions of the n-back task between various areas including the left hippocampus and the frontal poles with structures such as the caudate, occipital cortex, lingual gyrus and the temporal lobe.

Conclusion: Our pilot study showed that iTBS treatment may not be an effective tool for improving behavioural performance on the n-back task. However, the significant functional connectivity changes suggest that iTBS may be responsible for beneficial brain changes in depressed patients. These changes could be explained by increased efficiency and/or cognitive control in the context of the n-back task. Future research with sham controlled design and different working memory tasks are needed to determine the effects of iTBS treatment on WM.

Co-Authorship

Dr. Roumen Milev of the Department of Psychiatry at Queen's University contributed to the study design, funding and editing of this document.

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Table of Contents

List of Figures

List of Tables

List of Abbreviations

APA: American Psychiatric Association
BP: Bipolar disorder
BDI: Beck Depression Inventory
BDNF: Brain-derived neurotrophic factor
CGI: Clinical Global Impression Severity Scale
DBS: Deep brain stimulation
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition
dTMS: Deep Transcranial Magnetic Stimulation
ECT: Electroconvulsive therapy
FC: Functional Connectivity
fMRI: Functional magnetic resonance imaging
HDRS: Hamilton Depression Rating Scale
HPA axis: Hypothalamic-pituitary-adrenal axis
HSREB: Health Sciences Research Ethics Board
iTBS: Intermittent theta burst stimulation
MAOI: Monoamine oxidase inhibitor
MDD: Major depressive disorder
MDE: Major depressive episode
MTG: Middle Temporal Gyrus
rTMS: Repetitive transcranial magnetic stimulation
SD: Standard deviation
SNRI: Serotonin-norepinephrine reuptake inhibitor
SSRI: Selective serotonin reuptake inhibitor
TCA: Tricyclic antidepressant
TRD: Treatment Resistant Depression

Chapter 1: Introduction

The purpose of this chapter is to review the current knowledge and provide background information on major depressive disorder and the associated treatments. The overarching theme of this chapter is brain networks; focus is given to the neural networks involved in the mood and cognitive symptoms of depression, and therapeutic treatments like iTBS. Finally, the overlap between the networks, and the implications of these interactions are discussed.

1.1 Major Depressive Disorder

MDD is characterized by one or more major depressive episodes (MDE), with significant changes in mood/affect and cognition lasting two or more weeks. Specifically, there must be either depressed mood or a loss of interest or pleasure as one of the main symptoms. Four secondary symptoms must be met in order for an individual to be diagnosed with MDD. These symptoms include significant changes in weight/appetite, sleeping patterns, psychomotor activity, low energy, poor concentration/decisiveness, feelings of worthlessness or guilt, or thoughts of death or suicide (APA, 2013). Studies have also consistently documented higher rates of depression among women than among men: the female-to-male ratio averages 2:1 (APA, 2013).

It is clear that the course of MDD can be quite variable, but in most cases, individuals have recurrent MDEs with periods of remission in between. In fact, the majority of patients experience more than one episode in their lifetime (APA, 2013). Notably, with each recurrence, individuals are more likely to have subsequent episodes, and the time to the next recurrence is shorter (Keller & Boland, 1998). The differences in these characteristics of MDD, results in different subtypes of depression, one being persistent depressive disorder. Persistent depressive disorder has many of the same diagnostic criteria as MDD. However, persistent depressive

disorder is more chronic, with the depressed mood lasting for two or more years (APA, 2013). The lifetime prevalence worldwide is 3.6% of individuals (Bland, 1997). Due to the chronicity of this disorder, it poses as a severe impairment to the patients' everyday functioning. Treatment resistant depression is another subtype of MDD, where patients do not respond adequately to courses of at least two antidepressants. This resistance could be due to early discontinuation of treatment, insufficient dosage of medication, patient noncompliance, misdiagnosis, and concurrent psychiatric disorders (Sourey & Papakostas, 2006). Treatment-resistance is relatively common in cases of MDD. Rates of total remission following antidepressant treatment are only 50.4%. In cases of depression treated by a primary-care physician, 32% of patients partially responded to treatment and 45% did not respond at all (Papakastas & Fava, 2010). Therefore, alternative options like stimulation treatments (i.e., rTMS and ECT) and psychotherapy have been prescribed for treatment resistant depression. Clinical studies have demonstrated treatment success with these secondary treatments in both MDD and subtypes of MDD (Carpenter et al., 2012; Euba et al., 2015).

In terms of both prevalence and disease burden, MDD is one of the biggest modern public health concerns (Greden, 2001). According to Statistics Canada's 2012 Canadian Community Health Survey (CCHS) on Mental Health, 4.7% of the Canadian population aged 15 years and over reported symptoms that met the criteria for a major depression in the previous 12 months. Further, 11.3% of the population identified symptoms that met the criteria for depression at some point during their lifetime. Depression is a multi-symptomatic disorder, therefore causing significant distress and impairment in social, occupational, educational and other important areas of functioning (Judd et al., 1996). According to the World Health Organization,

it is the fourth leading cause of disability adjusted life years in the world, and it is identified as the fourth-ranked cause of premature death worldwide as well (Murray & Lopez, 1996).

Depression also has a major impact on the mental health of family members and caregivers, often with an increased presence of depression and anxiety symptoms. At the individual and family level, the loss of income and cost of medication create further strain on the family. On a macro scale, depression affects the Canadian economy because of the associated loss of productivity in the workplace due to absenteeism and diminished effectiveness, seconded with the high health care costs attributable to primary care visits, hospitalizations and medication (Public Health Agency of Canada, 2002). Apart from financial strains, social pressures such as the stigma against individuals with mood disorders has a major influence in determining whether an individual seeks treatment, takes prescribed medication or attends counselling. This effect is greater among men than women. The stigma also influences the successful re-integration of the individual into the family and community.

It is clear that depression is a multi-dimensional disorder with many clinical and socioeconomic challenges. Thus, early diagnosis and successful treatments are of the utmost importance for improving the patient's quality of life.

1.1.1 Depression and the Whole Brain

Depression is a disorder that includes many different symptoms, therefore a whole-brain approach is necessary for understanding the pathophysiology of this disorder. It has been proposed that major depressive symptoms are associated with the dysregulation of distributed neuronal networks encompassing multiple cortical and limbic regions rather than a single region (Davidson et al., 2002; Drevets, 2008; Mayberg, 1997, 2003; Phillips et al., 2003). PET and

fMRI studies have postulated that the ventral and dorsal subsystems of these brain networks are differentially affected in depression (Drevets et al., 2008; Mayberg, 2003). An imbalanced functional integration of these subsystems could lead to a heightened response to negative information in the ventral regions (bottom–up), and a failure to regulate the responses through the dorsal regions (top–down) (Phillips et al., 2003).

These subsystems consist of different brain areas, and the connections between the areas are altered by the different disorders; in depression, several studies have shown abnormal functional connectivity (FC) during both cognitive and emotional task paradigms (Chen et al., 2008; Johnstone et al., 2007; Matthews et al., 2008; Urry et al., 2006). These studies have provided valuable insights on how dysfunctional interactions between brain regions may relate to abnormal behavioral response patterns in depressed patients. Apart from task related brain activations, resting-state fMRI scans have also found large-scale connectivity patterns in the brain (Biswal et al., 1995; Fox and Raichle, 2007; Lowe et al., 1998).

In major depression, resting state studies have suggested altered FC in several areas within the network model of depression (Drevets et al., 2008; Mayberg, 1997). Decreased connectivity of the dorsal anterior cingulate cortex (ACC) with the medial thalamus and left pallidostriatum was found in patients suffering from depression (Anand et al., 2005). In another study, depressive patients were found to show increased connectivity of the subgenual ACC and the thalamus within the default mode network (DMN) (Greicius et al., 2007). Researchers have also found increased intra-network connectivity in depression between regions of the DMN, and within the task positive network (TPN), together with increased anticorrelations between regions of the two networks (Zhou et al., 2009). The default mode network is a stable and robust network found during resting state scans, and is often used as a point of comparison between groups; the

task positive network in the DMN is associated with attention and working memory (Fox et al., 2005). On the other hand, a study did not show any FC differences between major depressive disorder (MDD) patients and controls using conventional statistics, but the authors suggested that this could be due to the statistical analysis used (Craddock et al., 2009). Overall, the altered FC found in several task-related fMRI studies, and resting state findings further support the idea of dysfunctional interactions as a core feature of depressive symptomatology.

Most resting state fMRI studies on depression have found differences between the patient population and the controls in predefined regions or networks of interest, while some recent studies took a whole-brain approach to capture any meaningful differences between the groups. Some studies have identified several other networks of simultaneously oscillating brain regions (Beckmann et al., 2005; Damoiseaux et al., 2006), which may represent other functional domains associated with depression. In a study by Veer and colleagues (2010), they took an exploratory approach by using whole-brain resting state fMRI scans to discover all network differences between the medication-free depressed group and matched healthy controls. They found abnormal functional connectivity between different brain regions within three resting-state networks in depression. Some of these connections were well established in the literature, while others were not previously associated with major depression; a whole-brain activity study in 2012 by Zeng et al., also found similar results. Overall, future research is needed to determine if these connections relate to abnormal affect regulation and/or mild cognitive deficits, and how they affect these key symptoms associated with depression.

1.1.2 Working Memory

Working memory (WM) has been described and discussed as a cognitive system for temporary storage and manipulation of remembered information (Baddeley, 1986) and, more

specifically, as a process by which a remembered stimulus is held "on-line" to guide present behavior (Goldman-Rakic, 1996). In general, working memory is a fundamental set of processes that is integral to many cognitive operations, from complex decision making to selective attention (Baddeley, 1986). The cognitive functions involved in working memory may vary slightly depending on the task parameters, however, key processes like attention, encoding, storage, inhibition, and recall are consistently activated in WM tasks (Miyake et al., 2000). Past studies have linked these processes to different areas of the brain, and WM has shown to produce certain activation patterns involving these areas (Cohen et al., 1997; Greicius et al., 2003; Hampson, 2006).

Studies have shown that patients with frontal lobe damage are impaired on some but not all working memory tests, and in some cases deficits have been shown to relate to the inefficient use of organizational strategies that improve performance in healthy controls (Owen et al., 1996; Petrides and Milner, 1982). The prefrontal cortex (PFC) have been linked to WM since the 1930s, through the work of Jacobsen (1938). They showed that monkeys with lesions to the PFC had impaired spatial working memory. Part of working memory is keeping the information "online" in the brain for future use in a task. Fuster (1973) found neurons in the PFC that fired during these "online" periods, suggesting that they were involved in representing stimuli while it was not physically present. Later research has shown similar activation in neurons in the posterior parietal cortex, the thalamus, the caudate, and the globus pallidus (Ashby et al., 2005).

In human studies, it has been found that the lateral prefrontal cortex contributes to the strategic control of working memory processing, different from the idea of a storage function proposed initially (Owen et al., 1996; Petrides and Milner, 1982). The mid-ventrolateral frontal cortex is another area involved in WM (Owen et al., 1996). Interestingly, the mid-ventrolateral

frontal cortex has also been shown to be activated in tasks that require selection, comparison, and judgment of stimuli held in short- and long-term memory (Petrides, 1994), task switching (Dove et al., 2000) and stimulus selection (Rushworth et al., 1997). Unsurprisingly, these functions and abilities are also needed in WM. Imaging studies have found a role for right ventrolateral prefrontal cortex in WM, specifically in behavioral inhibition (Garavan et al., 1999; Konishi et al., 1999). Outside of the frontal cortex, the bilateral and medial premotor cortex have been found to be related to the maintenance of visuospatial attention during working memory, a process that is likely to be particularly important where delays are imposed between a stimulus and a response to that stimulus (Owen, 2000). Activation in the left dorsal aspect of the inferior parietal cortex has been observed frequently in response to the working memory load (Ravizza et al., 2004). Ravizza and colleagues concluded that the dorsal inferior parietal cortex may be important for retaining temporal information, for attentionally reactivating sources of information in neural regions, and/or for rapid switching of attention. Thus, this region has emerged as a major cluster in the current analyses of working memory studies using the n-back task.

Brain imaging has also revealed that working memory functions are not limited to the PFC, however, the functions of these brain areas are still being debated and researched (Mottaghy, 2006). One way to learn more about WM is by studying it through the pathological lens. Working memory deficits have been noted in multiple disorders, one being depression. There is a general agreement that memory deficits are common for patients with major depression (Caine, 1981; Cronholm & Ottosson, 1961; Sternberg & Jarvik, 1976; Stromgreen, 1977; Weingartner & Silberman, 1982), however the underlying mechanisms are still uncertain. Some studies have concluded that the primary defect is in the initial registration of information

(Cronholm & Ottosson, 1961; Sternberg & Jarvik, 1976), while others have reported that recall and learning on repeated presentation are poor (Goodwin, 1997). Depressive disorder affects the acquisition, memorization and retrieval of effortful information, but spares automatic learning (Caine, 1981; Cohen et al., 1982; Raskin et al., 1982; Weingartner and Silberman, 1982), thus, WM deficits may be linked to disruptions in executive function and attentional mechanisms. This is consistent with the association between depressive mood and activity in the prefrontal and cingulate cortices, as they are key areas for cognitive control (Mesulam, 1981; Posner et al., 1988; D'Esposito et al., 1995; McCarthy et al., 1996; Cohen et al., 1997; Courtney et al., 1997). A study by Pelosi et al. (2000) using event-related potentials (ERP) provided objective neurophysiological evidence for the impairment of WM in major depression. They concluded that the WM deficits found in depressed patients could be due to the dysfunction of the brain areas relevant to the central executive control system. It is clear that WM is affected by depression, however future research is needed to learn more about the specific involvement of the implicated brain areas and their interactions with each other during WM.

1.1.3 N-back Task

The N-back task was originally introduced by Kirchner (1958) as a visuo-spatial task and in 1990 Gevins et al. introduced it to the field of neuroscience by using it as a visuomotor memory task. The basic form of the task involves showing participants a series of stimuli, and the participants should respond when the current stimulus matches the stimulus that occurred N positions ago; the numerical value of N indicates the number of positions back in the sequence. The task involves multiple mental processes, such as the encoding of the incoming stimuli, the monitoring, maintenance, and updating of the material, as well as matching the stimuli. Higher level functions like decision making, selection, inhibition, and interference resolution are also

involved (Jonides et al., 1997). The nature of the task requires the execution of all these processes simultaneously, especially the simultaneous storage and processing of the material, which classifies N-back task as a working memory (WM) measure (Jonides et al., 1997; Kane & Engle, 2002).

Performance on the N-back task seems to involve processes that go beyond working memory. The cognitive control network is known to be activated due to the involvement of processes like inhibition and interference resolution (Kane, Conway, Miura, & Colflesh, 2007). Other complex processes include executive functions and attention shifting (McElree, 2001; Verhaeghen & Basak, 2005; Verhaeghen, Cerella, & Basak, 2004). Interestingly, past studies even showed correlations between N-back performance and various intelligence measures (Friedman et al., 2006, 2008; Gevins & Smith, 2000; Salthouse, Pink, & Tucker-Drob, 2008; Shelton et al., 2009; Van Leeuwen et al., 2007; Waiter et al., 2009). Therefore, the N-back is a task that evokes many different related cognitive modalities which matches the multiple cognitive processes involved in WM (Miyake et al., 2000; Salthouse et al., 2003; Stuss et al., 2002).

One of the most popular measures of working memory in neuroimaging literature is the N-back task (Conway et al., 2005; Kane & Engle, 2002). The reason to prefer the N back task over traditional WM span tasks in fMRI studies lies in the appealing way to manipulate WM load and in its response requirements, which are less complex than in standard WM capacity tasks (Conway, Kane, & Engle, 2003). It has been shown that the processing load can be varied systematically by manipulating the value of N, which is expressed with changes in accuracy and reaction time (RT) on the task (Jaeggi et al., 2010; Owen et al., 2005). The results from neuroimaging studies are also consistent in revealing reliable activation increases in selected

cortical areas with increasing processing load on the N-back task (Drobyshevsky, Baumann, & Schneider, 2006; Owen, McMillan, Laird, & Bullmore, 2005). The areas most commonly showing this load-dependent activation change are primarily located in bilateral prefrontal and parietal cortices. These main areas of activation have been observed independent of the stimuli variation of the N-back (Nystrom et al., 2000; Owen et al., 2005; Ragland et al., 2002; Schumacher et al., 1996), however, stimulus-specific regions are also known to be selectively activated (Knops, Nuerk, Fimm, Vohn, & Willmes, 2006; Owen et al., 2005). A meta-analysis study showed activation in multiple areas during the N-back task, including the lateral premotor cortex, dorsal cingulate and medial premotor cortex, dorsolateral and ventrolateral prefrontal cortex, frontal poles and medial and lateral posterior parietal cortex (Owen et al., 2005); and more areas are being researched. Overall, there are variations in the areas of activation during the N-back task between studies; more research is needed to better understand the functional specializations of each of these cortical components in working memory.

1.2 Depression Treatments

There are many types of treatments for depression; psychotherapy, pharmacotherapy, or a combination of both are the usually the main recommended treatments (APA, 2013). Other treatments such as electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS) are used as adjunct treatments, and can also be effective. Even with a selection of treatments, individuals with depression do not always receive adequate alleviation of their condition. Forty-four percent of people suffering from MDD do not seek treatment (Kessler, Merikangas & Wang, 2007), and for those who do seek treatment, few receive appropriate treatment for a sufficient length of time (Hirschfeld et al., 1997). There are many

reasons for inadequate treatment, including failure to recognize symptoms, underestimation of severity, misdiagnosis, and/or stigma (Hirschfeld et al., 1997; Greden, 2001).

Antidepressants are used as first line treatments and are relatively effective in the short-term; however, without continuous maintenance treatment, relapses tend to occur. Unfortunately, one in four patients who recover will relapse within 12 weeks of recovery (Keller, Shapiro, Lavori, & Wolfe, 1982). Recovery rates also decline steadily with length of episode, where only 50% of patients recover within six months, and 11.5% of patients remain ill even after five years (Keller et al., 1982). Cases of depression, where the individual does not respond adequately to treatment, are termed treatment-resistant depression. Treatment-resistant depression is associated with poor clinical outcomes and impaired long term functioning (Cusin & Dougherty, 2012). For example, there is an increased risk of mortality, both from suicide and from general medical comorbidities (Lisanby, 2007) in this type of depression. Despite a variety of treatment options, some individuals with MDD will continue to experience debilitating mood and cognitive symptoms. Thus, exploration and discovery of treatment options for MDD are needed, especially for individuals with subtypes like persistent treatment resistant depression.

1.2.1 Pharmacological Treatments

Pharmacological treatment remains the most studied and best evidenced treatment for MDD, and is often the default treatment. Pharmacological treatments like antidepressants are generally effective for both acute treatment and relapse prevention in depression (Greden, 2001), though there is some debate as to effectiveness in the clinical setting (Dimidjian et al., 2006; Moncrieff & Kirsch, 2005). There are different classes of antidepressants. The Canadian Network for Mood and Anxiety Treatment (CANMAT) guidelines propose SSRIs, SNRIs and the newer ‘second-generation’ agents as first-line options for the management of MDD because

they have better safety and tolerability profiles than older medications (Lam et al., 2009). The second-line treatment options include the TCAs, trazadone and quetiapine XR. Tricyclic antidepressants are recommended as second-line antidepressants because of tolerability and safety issues. Trazodone is also considered a second-line antidepressant because it is very sedating at therapeutic doses, therefore, it is also often prescribed for sleep disturbances in MDD. Quetiapine XR also falls under the second-line antidepressant category due its tolerability profile and relative lack of comparative data with SSRIs and second-generation antidepressants. After second-line treatments have failed, treatment options include the monoamine oxidase inhibitors (MAOI) which are recommended as third-line because of tolerability and safety issues, and dietary and drug restrictions. A meta-analysis by Arroll et al. (2005) found that both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are effective for treating depression, compared to placebo. In fact, there is comparable effectiveness for the various classes of medications, including TCAs, SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), buproprion, and monoamine oxidase inhibitors (MAOIs; APA, 2013).

It is known that newer antidepressants, such as SSRIs, provide advantages in tolerability over antidepressants such as TCAs. However, even within the SSRI class, differences in efficacy or tolerability exist between individual drugs (Sanchez, Reines, & Montgomery, 2014). In a comprehensive analysis of remission with venlafaxine versus SSRIs, a modest advantage to fluoxetine was noted (Nemeroff et al., 2008). Kennedy and colleagues (2009) conducted a meta-analysis of 16 randomized controlled trials and reported superior efficacy for escitalopram compared to other SSRIs and SNRIs. Also, a meta-analysis integrating both direct and indirect comparisons of the efficacy and acceptability of 12 new-generation antidepressants showed a small superiority in response rates for escitalopram, mirtazapine, sertraline and venlafaxine

compared to the others (Cipriani et al., 2009). Another meta-analyses of randomized, controlled trials (RCTs) comparing antidepressant treatments concluded that clomipramine, escitalopram and venlafaxine had definite superiority, while duloxetine, milnacipran and mirtazapine had probable superiority against SSRI comparators (Montgomery et al., 2007).

It is clear that there is an abundance of antidepressant medications for the treatment of MDD, however, an on-going significant challenge involves selecting the antidepressant medication or combination of medications that is most likely to lead to a response for the patient. This challenge is exacerbated in treatment-resistant depression (TRD), which is defined as a lack of improvement in symptoms (i.e., 20% reduction in depression scores) following adequate trials of two or more antidepressants. Pharmacological strategies for TRD include switching to a different antidepressant monotherapy, or adding another agent to the first antidepressant. In some cases, augmentation (adding a medication that is not considered an antidepressant (e.g., lithium or thyroid hormone)) or combination (adding a second antidepressant to the first (Lam et al., 2009)) may be used. In practice, it has been well documented that approximately 6-8 weeks of "watchful waiting" are required to observe full recovery with a certain medication (Bauer et al., 2007; Fochtmann & Gelenberg, 2005). Subsequent treatments that are utilized either alone or in combination further extend the period of watchful waiting. Unfortunately, early discontinuation rates of antidepressant treatments are high with about 30% of patients discontinuing medications within 30 days and more than 40% discontinuing within 90 days (Olfson et al., 2006). This is often due to the lack of response or remission from the medication. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study demonstrated that less than 50% of depressed patients respond to the first antidepressant they try and even less patients (30%) achieved full remission (Trivedi et al., 2006). The probability that an individual will achieve

remission decreased steadily with each new treatment failure. Patients who fail to achieve full remission have a more recurrent and chronic course of illness, increased medical and psychiatric co-morbidities, greater functional burden, and increased social and economic costs (McIntyre and O'Donovan, 2004). Hence, the management of depression remains a constant challenge in clinical practice, largely due to the fact that initial pharmacological treatments frequently do not lead to remission and recovery. In these cases, alternative treatment options can be explored, including stimulation treatments such as ECT or rTMS. Studies have found that both ECT and rTMS are effective for treating MDD, and give similar lasting clinical benefits (Dannon, Dolberg, Schreiber, & Grunhaus, 2002; Martin et al., 2002).

1.3 Transcranial Magnetic Stimulation

The first stable TMS devices were developed around 1985 by Anthony T. Barker (Horvath et al., 2011; Noohi & Amirsalari, 2016). They were originally intended as diagnostic and research devices, and therapeutic uses are still being explored today. The mechanism behind TMS resolves around the quickly discharging current from a large capacitor into a coil to produce pulsed magnetic fields (Walsh & Pascual-Leone, 2003). The magnetic field pulses can either depolarize or hyperpolarize neurons in the target brain areas, therefore creating excitatory or inhibitory effects. Building on the basic mechanisms of TMS, scientists have continued to manipulate the parameters to optimize the therapeutic potential. One variation like repetitive TMS produces longer-lasting effects in the brain which persist past the initial period of stimulation. Interestingly, rTMS can increase or decrease the excitability of the corticospinal tract depending on the intensity of stimulation, coil orientation, and frequency, which gives it great treatment flexibility (Kaneko et al., 1996).

TMS has been used for evaluation and/or treatment in many different disorders, spanning from motor related disorders to psychiatric ones (Groppa et al., 2012). As of October 2008, the US Food and Drug Administration authorized the use of rTMS as a treatment for clinical depression (Slotema et al., 2010). It is often prescribed as an adjunct treatment or a second line treatment for patients with treatment resistant depression. TMS is generally regarded as safe for a variety of different patient populations, including adolescents (D'Agati, Bloch, Levkovitz & Reti, 2010). Like all treatments, there are some possible side effects; the greatest risk is the rare occurrence of fainting and even less common, induced seizures (Fitzgerald, 2013; Rossi et al., 2009). Other adverse short-term effects of TMS include transient pain or discomfort, cognitive changes, and/or hearing loss.

rTMS treatment have been well received as a therapeutic tool for MDD because of its non-invasive nature compared to other stimulation treatments like ECT, and its minimal side effects. However, one of the remaining concern and interest for rTMS is its effects on cognition. Many rTMS trails have been conducted in patients with depression over the past 15 years to better understand the safety and tolerability (Bakker et al., 2015; D'Agati, Bloch, Levkovitz & Reti, 2010; Guse, Falkai & Wobrock, 2010); most of these trials used high frequency stimulation (>1 Hz) applied to the left dorsolateral prefrontal cortex (DLFPC). Meta-analyses of these trials showed an overall antidepressant effect with a two week course of high frequency TMS than with sham treatment (Schutter, 2009). Studies have also looked at individual modalities of cognition and found inconsistent but mostly positive results for rTMS on working memory, attention, executive functioning, and processing speed, however the magnitude of improvement have been moderate (Guse, Falkai & Wobrock, 2010; Preston et al., 2009). Furthermore, a review study has shown that the relapse rates after rTMS treatment could be quite high (Berlim

et al., 2014). One of the main reasons for the mixed findings in the literature is due to the variety in the stimulation parameters, sites and patient populations (i.e., diagnoses and demographics).

Several attempts have been made to improve the efficacy of rTMS. For example, a study has investigated the effects of low-frequency (≤1 Hz) rTMs applied to the right DLPFC (Li et al., 2013). Others have used bilateral rTMS, with greater treatment duration (Fitzgerald et al., 2011; Loo et al., 2003). Although most of these studies did not find significant improvement in efficacy compared to the standard rTMS stimulation course, however, the change in duration did increase the response rate to more than 50%. Continuous efforts are being made to improve the TMS treatment, with studies investigating the use of neuronavigation (Ahdab et al., 2010), priming (Iyer, Schleper & Wassermann et al., 2003), and a subtype of TMS with different parameters known as theta burst stimulation (Chistyakov et al., 2010; Grossheinrich et al., 2009). The current challenge of TMS treatment is to establish the optimal stimulation protocol and parameters for delivery of the technique for the intended disorder.

1.3.1 rTMS vs. iTBS

In the last two decades, repetitive transcranial magnetic stimulation has been studied as a therapeutic tool in several neuropsychiatric disorders, primarily for the treatment of major depression where it has shown a consistent and reproducible therapeutic effect (Feinsod et al. 1998; George et al. 1997; Pascual-Leone et al. 1996). In general, high-frequency rTMS transiently facilitates cortical responses (Pascual-Leone et al. 1994) while low-frequency rTMS inhibits cortical excitability (Chen et al. 1997). However, these effects have typically been short lasting, of moderate size and variable. This calls for the design of a more effective rTMS paradigms that will achieve a robust antidepressant effect. Studies on the motor cortex using TBS showed that it produced more robust and enduring changes in cortical excitability than tradition

rTMS (Huang et al. 2007, 2009; Ishikawa et al. 2007; Katayama & Rothwell, 2007). The application of this paradigm allows induction of long-lasting excitatory and inhibitory changes in cortical excitability. Intermittent theta burst stimulation have been shown to produce a long-lasting faciliatory effect on the motor cortex (Huang et al. 2005). These changes were shown to be consistent and robust across subjects. Thus, theta-burst TMS seems to offer an advantage to some of the shortcomings of conventional rTMS.

Another benefit of iTBS over rTMS is the elimination of a lengthy protocol, which significantly limits the number of patients who can be treated per day per device. The average treatment time for rTMS is approximately 35 min, while it is only around three to six minutes for iTBS. A chart review study compared the standard dorsomedial prefrontal cortex rTMS with iTBS (Bakker et al., 2015). Researchers found that there was no difference in the number of adverse events or the discontinuation rates between groups. There were also no group differences in pre-treatment or post-treatment scores, or percentage of improvements between groups. Therefore, the iTBS protocol with the same effectiveness but shorter duration could permit up to five-fold increases in treatment capacity, which in turn would permit lower treatment charges. Such improvements greatly facilitate wider affordability and possible adoption of iTBS as a mainstream treatment for MDD.

1.3.2 TBS and Depression

Theta burst stimulation (TBS) treatment is a welcomed addition to the therapeutic armamentarium, as one third of patients with depression are refractory to normally adequate dosages of antidepressants (Rush, 2007; Fekadu et al., 2009) and in need of a more powerful treatment option. Efficacy aside, the safety and tolerability of brain stimulation has always been of interest. The main concern about potential adverse effects of these treatments is their ability to

induce seizures. Huang et al. (2005) were the first to describe the safe application of magnetic TBS of the motor cortex in humans. Their stimulation protocol consisted of 600 stimuli given continuously or intermittently at an intensity of 80% aMT. Studies that followed used similar stimulation parameters. Grossheinrich et al. (2009) reported the safe application of intermittent and continuous TBS at 80% rMT intensity over the DLPFC and medial PFC in healthy subjects, with minor effects on neuropsychological measures and no impact on mood. Li et al., 2014 increased the intensity from 90% to 100% aMT and found no evidence of seizures or any other significant adverse effects. Only one patient requested to withdraw due to local painful sensation in the stimulated area. These findings suggest that TBS treatment can be applied safely in a wide range of stimulation parameters; however, further work needs to be done to consolidate the safe boundaries for iTBS.

With iTBS being a relatively safe treatment, studies have turned to unravel the therapeutic potential and mechanisms of this treatment. An open label study by Chistyakov and colleagues reported clinical improvement after two weeks of treatment to the left prefrontal intermittent TBS and right prefrontal continuous TBS (Chistyakov et al., 2010). This study showed preliminary evidence that different parameters of TBS is effective in treating depression, and also demonstrated some dose-dependent effects of TBS. Continuous TBS was significantly more effective for lessening depression than intermittent TBS, however the methodology used to measure these effects could affect the results. A pilot study investigated the antidepressant efficacy of the bilateral prefrontal TBS and found that active TBS was more effective than sham TBS (Plewnia et al., 2014). Positive results were shown again for TBS in a recent randomized sham controlled study looking at the efficacy of prefrontal theta-burst stimulation on refractory depression (Li et al., 2014). The researchers used three different types of TBS: continuous,

intermittent and combined. They found an antidepressant response for all three types of TBS after two weeks of treatment compared to the sham group. The mean antidepressant effect was the highest in the combined group followed by the intermittent group then the continuous group. Therefore, theta burst stimulation is well tolerated and has good efficacy in treating depression, however, there are variations in effectiveness based on the TBS parameters and the depression subtypes.

In terms of mechanism, intermittent TBS can induce lasting effects through long-term potentiation-like effects on neuronal synapses. Most of the evidence for iTBS mechanisms comes from studies on the motor cortex. It has been shown that intermittent TBS could increase cortical excitability, while continuous TBS could decrease cortical excitability (Huang et al., 2005). In an investigation of iTBS mechanisms with fMRI, it has been found that iTBS targeting the motor cortex could not only affect blood perfusions at the stimulated motor cortex, but could also affect motor-related remote brain regions (Cardenas-Morales et al., 2011). Although the TBS mechanisms operating in the human motor cortex may not be completely transferred to other brain regions, such observations of the influence on both the stimulated cortical regions and the remote regions connected to them are consistent with rTMS findings in the treatment of major depression (Baeken and De Raedt, 2011). Studies using the high-frequency rTMS on the left dorsolateral prefrontal cortex show a cascade neurobiological changes in limbic regions linked with the stimulated prefrontal cortex, such as the anterior cingulate cortex, amygdala, and associated temporal cortical regions (Li et al., 2010; Baeken and De Raedt, 2011). The same mechanisms may be reflected in iTBS stimulation. At the molecular level, TBS might impact depressive symptoms through its effects on the glutamatergic, GABAergic systems, gene expression, and protein levels (Cardenas-Morales et al., 2010). The combination of these

mechanisms could be responsible for the therapeutic effects of iTBS on depression. More research is needed to explore the specific (i.e., depressive versus cognitive symptoms) therapeutic potentials of iTBS and the underlying mechanisms.

1.4 Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a neuroimaging procedure using MRI technology to measure brain activity (Huettel, Song & McCarthy, 2004). The signal detected by the fMRI scan is called blood-oxygen-level dependent (BOLD) contrast, which is based on the hemodynamic changes in the brain. The signal is based on the blood flow and blood oxygenation changes in the brain, which are closely linked to neural activity (Huettel, Song & McCarthy, 2004). When neurons become active, local blood flow to those brain regions increases, and oxygenated blood displaces deoxygenated blood around two seconds later. This process rises to a peak four to six seconds after the task stimulus is presented, which affects the temporal resolution of the fMRI (Huettel, Song & McCarthy, 2004).

There are some limitations to fMRI, one is that inhibitory and excitatory input to a neuron from other neurons cannot be distinguished, and both contribute to the BOLD signal. Within a neuron these two inputs might cancel out, and no signal may be detected even if that neuron was affected by the stimulus (Huettel, Song & McCarthy, 2004). There are also challenges with the interpretation and analysis of the fMRI signal. For example, the amplitude of the BOLD signal does not necessarily reflect the individual's behavioral performance. A complex cognitive task may initially trigger high-amplitude signals associated with good performance, but as the subject gets better at it, the amplitude may decrease while performance stays the same. This is expected to be due to increased efficiency in performing the task (Huettel, Song & McCarthy, 2004). BOLD signals are frequently corrupted by noise from various sources and hence different

statistical procedures are used to extract the underlying signal; this process is known as preprocessing. The five main sources of noise in fMRI are thermal noise, system noise, physiological noise, random neural activity, which could be caused by the scanner hardware of the subject. Thus, the statistical analyses used preprocess and to analyze the fMRI signal could impact the findings.

fMRI have been used in both clinical and research settings to provide insights into various neurological and mental disorders. It has also be combined with other brain imaging techniques such as transcranial stimulation and EEG (Bohning et al., 1999; Mulert et al., 2004). The combination of these different technologies helps to complement and supplement fMRI, and allow the production of spatially and temporally superior scans. These techniques are in development to help scientists to better understand the neurological workings of complex disorders like depression.

Chapter 2: Methods

2.1 Participants

Written informed consent was obtained following verbal explanation of the study. All materials and protocol were approved by the Queen's University Health Sciences Research Ethics Board (HSREB). All data were collected at Providence Care Hospital site and at the MRI Facility at Queen's University in Kingston, Ontario, Canada.

Patients were referred by the nursing staff at the ECT/TMS clinic at Providence Care Hospital. Ten patients between the ages of 18-70 were recruited from the ECT/TMS clinic at the Providence Care Hospital. All participants in the study have been diagnosed with unipolar or bipolar major depressive disorder (MDD). All participants had no changes in the psychotropic medication or dosage for at least four weeks before the start of the iTBS treatment. The

medication regimes of all participants were recorded, and followed throughout the study. For all participants, a pre-screening questionnaire was administered to ensure eligibility for the study. Only patients that passed the TMS safety screening and have not had a TMS scan within the last six months were approached. Patients were excluded if they have a history of substance dependence or abuse within the last three months and/or have active suicidal intent. Patients were also excluded if they have a concomitant major unstable medical illness, cardiac pacemaker or implanted medication pump and/or have a lifetime Mini-International Neuropsychaitric Interview (MINI) diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, or current psychotic symptoms. In accordance with the MRI and TMS safety regulations, patients were excluded if they have had a significant brain injury and/or have an intracranial implant (e.g. aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal object within or near the head, excluding the mouth, that cannot be safely removed. In order to reduce any confounding variables for the cognitive testing, patients were excluded if they have non-correctable clinically significant sensory impairment (i.e., cannot hear well enough to cooperate with interview) and/or have any neurodegenerative or developmental disorders/diseases. Active enrollment in the study ran for approximately 18 months.

2.2 iTBS protocol

iTBS was performed in accordance with the recommendations of the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation (Wassermann, 1998). Stimuli were applied using a MagPro X100 stimulator (MagVenture) and a standard butterfly coil (MFC-B65). The bursts were applied at a frequency of 5 Hz and consisted of seven 1 m stimulus trains separated by 1 min intertrain intervals, for approximately five minutes. The

stimulation target for the iTBS is the right and left DLPFC, and to pinpoint it for each individual, the primary motor cortex was used as a marker. The location of the motor cortex was identified by the lowest stimulator output resulting in a visible twitch of the left thumb. Participants received one iTBS session (approximately six mintues) per day for a total of 25 days, five days a week. The treatment is non-invasive with some participants experiencing light headaches and temporary hearing disturbances. There were no accidents nor adverse events reported.

2.3 Clinical Measures

To measure changes in the participants' depressive symptoms the following scales and questionnaires were used: Beck Depression Inventory-II (BDI; Dozois, Dobson, & Ahnberg, 1998) and Clinical Global Impression Severity Scale (CGI-S; Busner & Targum, 2007) and Montgomery Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979). The CGI-S and MADRS were clinician-rated, while the BDI was self-administered by the participant.

2.4 Functional Magnetic Resonance Imaging

fMRI data were acquired on a 3T MRI scanner (Siemens Trio, Siemens) using a gradient-echo echoplanar imaging (EPI) sequence with the following specifications: 28 slices, 3.5 mm slice thickness, 1 mm gap, TR: 2000 ms, TE: 30 ms, field of view: 68 x 68 mm, flip angle: 90°. The voxel size for the anatomical scan is 1x1x1 and for resting state and n-back is 1x1x3.5. There were three phases to the scan: anatomical scan, resting state scan and n-back task. The anatomical scan is 8 minutes, and the resting scan is 7 minutes, and the n-back task is 4.5minutes, for a total of 19.5minutes.

2.4.1 Resting State Scan

In the resting-state experiment participants were instructed to keep their eyes open, relax and do not engage in any particular mental activity during the scan (task duration: 7.0 min). After

each scan, investigators confirmed with the participant that they had not fallen asleep in the scanner.

2.4.2 Working Memory Measure

The 2-back task, a variation of the n-back task was used to measure working memory in this study (Bilek et al., 2013). The software called Presenation was used to run the task on a laptop, which was connected to a desktop computer controlling the MRI machine. This task uses a block design, by alternating between the 0-back and 2-back conditions. The 2-back condition is the working memory condition, while the 0-back condition acts as the control condition. There are four blocks for each condition, with a total of eight blocks. The task takes 4.5mins to complete.

For each trail, a random number between one and four will be shown at a set corner in a diamond-shaped box on the screen; only one number will flash up at a time. The presentation time of the number is 500 ms with an inter-stimulus interval of 1500 ms. In the control condition, participants are asked to press the key on the button box that corresponds to the number currently on screen. In the working memory condition, subjects are asked to encode a currently seen number and simultaneously respond with the button that corresponds to the stimulus presented two trials back. Participants are required to respond to every item. Notably, the spatial position of a given number remained constant over the experiment, i.e., the working memory task did not challenge the maintenance of the spatial relation of the presented stimuli. To make sure that the participants understood the task and that their performance accurately reflected their abilities, each individual was asked to practice the task before going into the MRI scanner (average number of practice trials: 2.5). All participants practiced until the accuracy for the last two

practice runs were not different by more than 5%. Practicing the n-back task before scanning is a common practice that have been used in past study (Bilek et al., 2013).

2.5 Procedure

Each participant was tested on a one-on-one basis with a researcher, and the order of test administration was the same for all participants. There were three visits in this study, the pre-screening visiting, the first testing visit before the start of the iTBS treatment and the last visit within two weeks following participant's last iTBS treatment. During the pre-screening visit, participants filled out the informed consent form and demographic and health questionnaire. Some time between the pre-screening visit and the first visit, participants were assessed by psychiatrists on the CGI and trained students on the MADRS. At the first testing visit, participants filled out the clinical measures, and the MRI safety checklist, practiced the n-back task, and completed the official n-back task inside the MRI scanner. The MRI scan was conducted by the MRI technician at Queen's University MRI Facility. The procedures for the first testing visit was repeated at the second testing visit, which was scheduled within two weeks of the last iTBS treatment to allow flexibility in scheduling. At the end of the second visit, participants received $30 for incidental expenses.

2.6 Clinical Measure Analyses

Statistical analyses of the clinical scales were done using SPSS (version 18.0; SPSS Inc., Chicago, IL). Descriptive statistics, paired t test and Wilcoxon Signed-Rank Test were conducted for the data collected from the two testing visits for the clinical scales and for the accuracy scores on the n-back task. Power analyses were done using G*Power (version 3.1.9.2; Faul et al., 2009) for the BDI scores to determine the number of participants needed to reach significance, BDI was chosen because it was the closest to significance out of the clinical measures.

2.7 MRI Data Analyses

The programs Matlab (version 8.0; Massachusetts, United States.) and Conn were used for all data preprocessing and analysis routines. The same preprocessing and analyses were done for the resting state and n-back task scans. Signals from grey matter were analyzed while signals from white matter and CSF were discarded. All images were realigned to the first image of the scan run, slice time corrected, and smoothed with a 9mm FWHM Gaussian filter. For activation analysis, images were normalized to standard stereotactic space (as defined by the Montreal Neurological Institute (MNI)) before smoothing. Resting state and n-back scans were superimposed onto the anatomical scans for all analyses.

2.7.1 Functional Connectivity Analyses

A hypothesis driven, seed to voxel analysis was done for the resting state and the n-back task scans. Seeds (6 mm sphere markers on a spatial location) were planted in areas of interest within the brain. The strength of connectivity between the seeds and other brain areas were determined, and significant connections were noted. The changes in the strengths of these connections between visit one and two were compared, with alpha set at $p \leq 0.05$. All connectivity differences were corrected for multiple comparisons.

Chapter 3: Results

3.1 Demographics Measures

Fifteen participants were recruited for the study, two participants did not complete time two, and three participants declined the MRI scan. Therefore, ten female and male participants completed the entire study, and their data were used for analysis. The mean age was 48.4 ± 13.18, with seven females and three males. All participants were diagnosed with major depressive disorder, with nine unipolar depression and one bipolar depression. Two participants

also had comorbid anxiety with one participant having comorbid PTSD. The average number of years of education is 16.4 ± 1.24; all participants had some education above high school. The average number of psychotropic medication the participants were on is 1.3 ± .95. The total number of prescription medication the participants were on is 3.2 ± 3.23. The drugs in the others category were non-psychotropic drugs, and included medications such as heart, stomach or thyroid medications. There were no changes in the psychotropic medication(s) for all participants throughout the study.

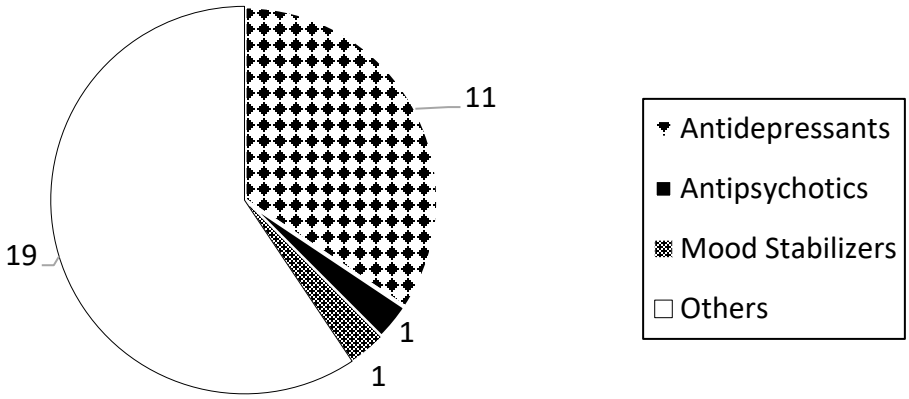


Figure 1. The breakdown of the number of medications taken by the participants during the study period. A total of 11 antidepressants, one antipsychotic, one mood stabilizer and 19 other drugs are taken by the ten participants.

3.2 Clinical Measures

Two depression scales (BDI and MADRS) and one physician assessment (CGI) were used to measure the mood symptoms of participants at time one and two of the study (Figure 2). There were no significant differences between time one and two for any of the measures. The nonparametric test Wilcoxon Singed Rank Test was for the BDI scores, because the data did not fit the normal distribution. BDI ($Z = -1.47$, $p = .14$). The paired t test was used to analyze the MADRS ($t(9) = -0.28$, $p = .79$) and the CGI ($t(9) = .39$, $p = .72$) because normal distribution was

met. A power analysis showed that a sample of 36 would be needed to reach a significance with an alpha level of .05 and an effect size of .64 (medium strength).

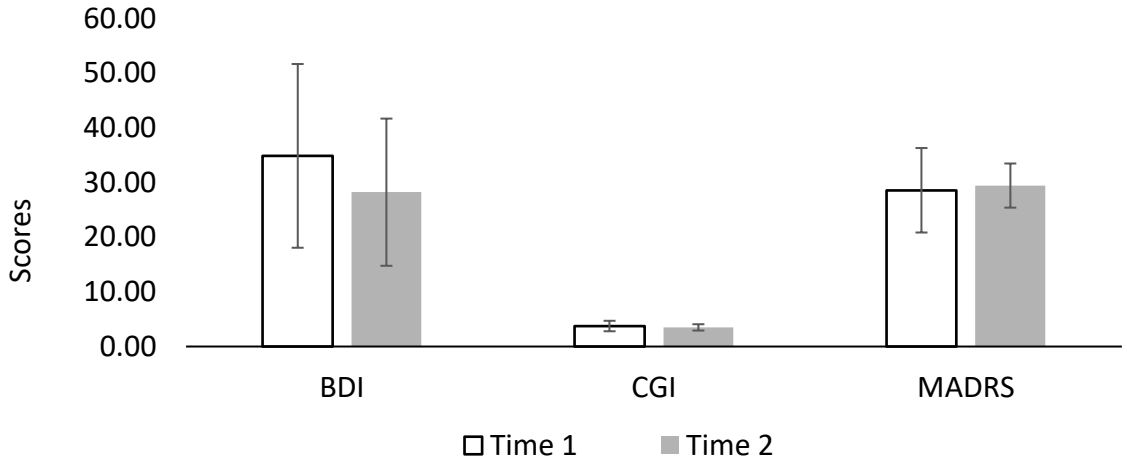


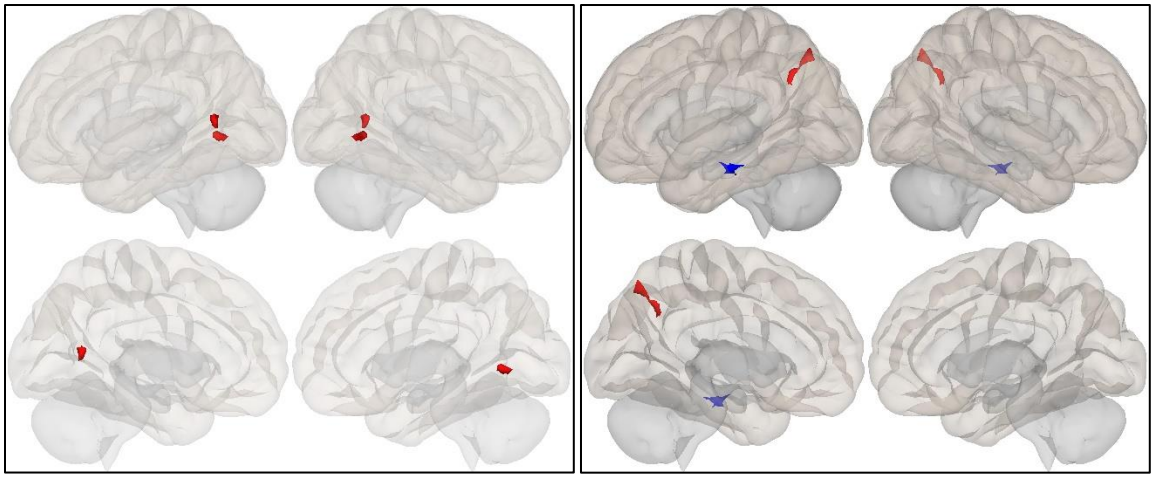
Figure 2. Both time 1 and 2 depression scale scores for participants. Individual scores (Mean ± SD); BDI: time 1= 34.86 ± 16.8, time 2 28.22 ± 13.46; CGI: time 1 = 3.75 ± .48, time 2 = 3.5 ± .29; MADRS: time 1 = 28.57 ± 7.72, time 2 = 29.43 ± 1.53.

3.3 MRI Analyses

Seed to voxel analyses were conducted for the resting state and both conditions of the n-back task, with specific seeds in relevant areas including locations in the prefrontal cortex and the hippocampus (Table 1). All statistics were corrected for multiple comparison, with alpha set at .05.

3.4 Resting State

There were three significant connectivity changes before and after the iTBS treatment. There was an increase in the connectivity between the left frontal pole and the lateral occipital cortex ($p = 0.002$). Also, an increase between the right frontal pole and the bilateral lingual gyrus ($p = 0.004$). There was also a decrease in connectivity between the left frontal pole and the middle temporal gyrus ($p = 0.006$).



A **B**

Figure 3. (A) Four perspective view of the activation during the resting state scans, with a seed in the right frontal pole. There is an increase in connectivity between the seed and the bilateral lingual gyrus (red areas) at the Time 2 compared to Time 1. (B) Activation during the resting state scans, with a seed in the left frontal pole. There is an increase in connectivity between the left frontal pole and the lateral occipital cortex (red area) and a decrease in connectivity with the middle temporal gyrus (blue) at Time 2 compared to Time 1.

3.5 n-back Task

Participants' accuracy scores (percentage) and reaction times on the n-back task before and after the treatment were calculated (Figure 2). There were no significant changes for the 0-back ($t(9) = -.57$, $p = .58$) and the 2-back condition ($t(9) = -1.53$, $p = .16$) for accuracy and reaction time: 0-back ($t(9) = -.86$, $p = .41$) and 2-back condition ($t(9) = .90$, $p = .35$) between time one and two. There was a significant difference in accuracy (%) between the 0-back and 2-back condition for both time points (time 1: $t(9) = 4.62$, $p = .002$; time 2: $t(9) = 4.05$, $p = .003$). This validates the load manipulation, proving that the 2-back condition requires more cognitive power.

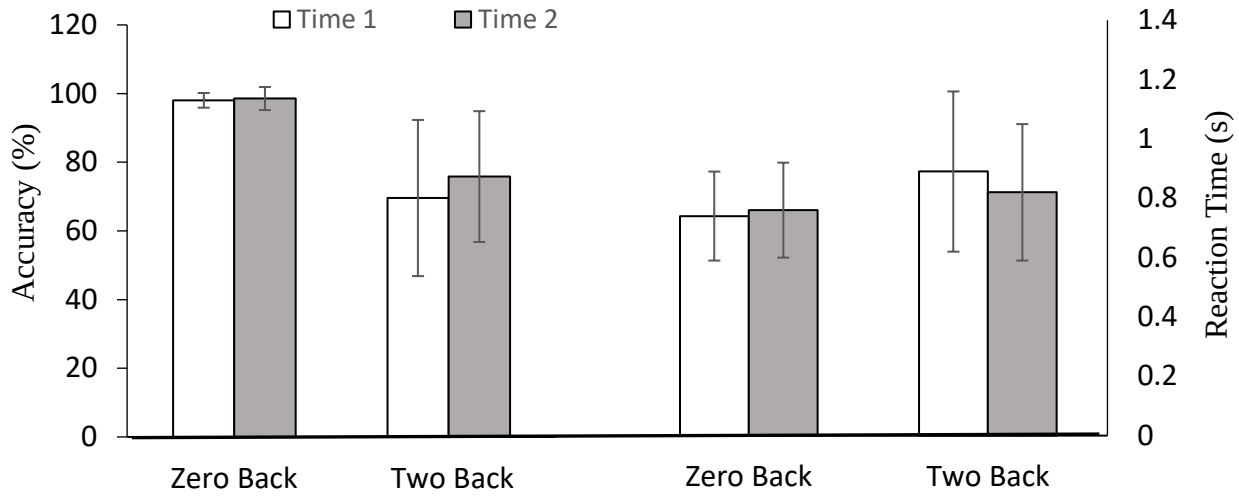


Figure 4. Time 1 and Time 2 accuracy (percentage) and reaction time (seconds) means for both zero back and two back conditions. Accuracy-Time 1: zero back (M = 98.03, SD = 2.14), two back (M = 69.58, SD = 22.74); Time 2: zero back (M = 98.57, SD = 3.36), two back (M = 75.83, SD = 19.05). Reaction Time-Time 1: zero back (M = .74, SD = .15), two back (M = .89, SD = .27); Time 2: zero back (M = .76, SD = .16), two back (M = .82, SD = .23).

Seed to voxel analyses were conducted for both conditions of the n-back task, with specific seeds in relevant areas including locations in the prefrontal cortex and the hippocampus (Table 1).

3.5.1 0-back Condition

There was an increase in the connectivity between the right hippocampus and the left caudate ($p = 0.01$).

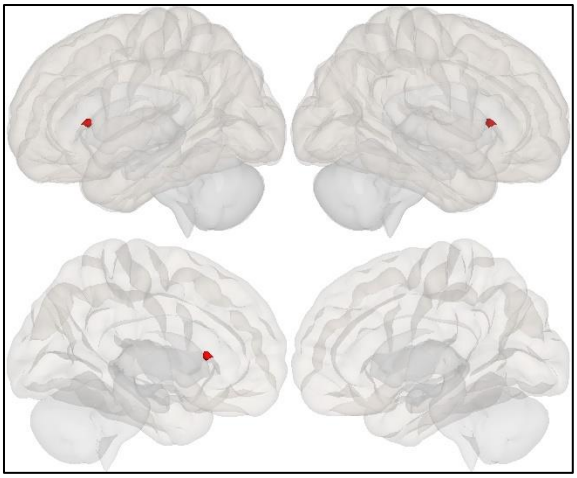
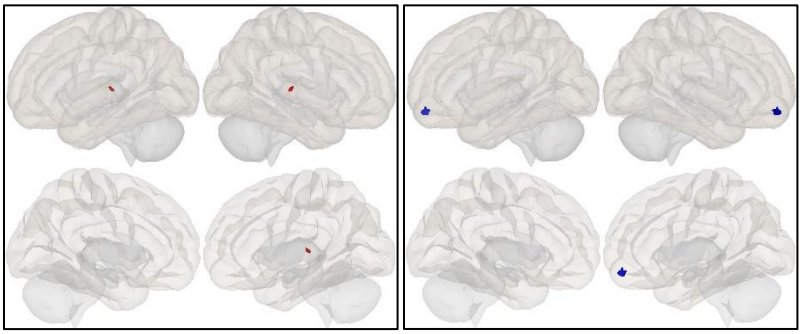


Figure 5. Four perspective view of the activation during the 0-back condition of the n-back task with a seed in the right hippocampus. There is an increase in the connectivity between the seed and the left caudate (red area) at Time 2 compared to Time 1.

3.5.2 2-back Condition

There was a decrease in connectivity between the right inferior frontal gyrus and the right frontal pole ($p = 0.001$). There was also an increase in connectivity between the left inferior frontal gyrus and the right superior frontal gyrus ($p = 0.04$).



A **B**

Figure 6. (A) Four perspective view of the activations during the 2-back condition of the n-back task with a seed in the left inferior frontal gyrus, and an increase in connectivity between the seed and the superior frontal gyrus (red area) at Time 2 compared to Time 1. (B) There is a seed in the right inferior frontal gyrus, and a decrease in connectivity between the seed and the right frontal pole (blue area) at Time 2 compare to Time 1.

Table 1. Statistical Values of the Significant Changes in Connectivity between Brain Areas

	Seed	*Connected To*	*Cluster Size (K Value)*	*Beta Value*	*T value*	*p-FDR value*
Resting State	Left Frontal Pole	Lateral Occipital Cortex	89	0.26	8.37	0.002
		Middle Temporal Gyrus	65	-0.25	-7.06	0.006
	Right Frontal Pole	Bilateral Lingual Gyrus	81	0.22	10.64	0.004
0-back	Right Hippocampus	Left Caudate	40	0.75	6.73	0.01
2-back	Right Inferior Frontal Gyrus	Right Frontal Pole	85	-0.65	-9.80	0.001
	Left Inferior Frontal Gyrus	Right Superior Frontal Gyrus	44	0.70	7.00	0.04

Chapter 4: Discussion

The aim of this pilot study was to investigate the effects of iTBS on working memory in patients with depression. Contrary to our hypothesis, there was no differences in n-back performance scores and depression scores before and after treatment. However, there were brain connectivity differences between relevant brain areas after treatment.

4.1 iTBS and Depression

There were no significant differences in the BDI, MADRS or CGI scores before and after the iTBS treatment. iTBS stimulation targets and/or sample size are possible explanations for these findings.

4.1.1 iTBS Stimulation Sites

The stimulation sites used in this study follows the approved iTBS protocol at the Kingston Providence Care Hospital. The sites are left dorsolateral prefrontal cortex and right dorsolateral prefrontal cortex. These sites are often used in iTBS studies, some studies use both sites while others use only one (Chistyakov et al., 2010; Grossheinrich et al., 2009). Although the

left and right dorsolateral prefrontal cortex are the standard areas stimulated in treatment, recent studies have shown these areas may not be the most therapeutic for some depressed patients (Downar and Daskalakis, 2013). A study by Drysdale et al., 2017 found that there are different brain activation patterns in depressed patients, and these patterns could be summed up into four "biotypes". Patients in different biotypes have different resting state brain activations that may translate to response differences for stimulation treatments. Downar and Daskalakis (2013) furthered supported this by discussing the merits of different stimulation sites apart from the DLPFC, such as dorsomedial prefrontal cortex (DMPFC), frontopolar cortex (FPC), ventromedial prefrontal cortex (VMPFC), and ventrolateral prefrontal cortex (VLPFC). Downar and Daskalakis proposed that these new targets may help to propel stimulation treatment across the threshold of efficacy required for a first-line treatment. Therefore, the patients in this study could belong to different biotypes, and that the bilateral dorsolateral prefrontal cortex stimulation used in this study may not be therapeutic for them; thus, no changes in depression scores. Future studies should explore different stimulation sites to help determine the most therapeutic site for each participant.

4.1.2 Sample Size

A power analysis (G*power) was conducted based on the depression score results to determine the number of participants needed to reach significance for this study. The G power analysis revealed that a sample of at least 36 people is needed to reach an alpha of .05 with a moderate effect size. This G power analysis was conducted using the depression results from the BDI measure, as it was the closest to reaching significance. The CGI and MADRS scores were even further from significance, suggesting that sample size is not the most important factor in

determining the effects of iTBS on depression; furthermore, even with a larger sample size, it is unlikely that all the depression measures will be significant.

4.2 iTBS and N-back

There were no changes in the performance (accuracy %) and reaction time on all conditions of the n-back task after iTBS treatment compared to baseline. This finding is different from our hypothesis but it is not completely surprising, as past studies have found mixed results. Some studies using the n-back task have found an improvement in reaction time but not accuracy (Owen et al., 2005), some found an improvement in both (Bilek et al., 2013), and some found no improvement in either (Matsuo et al., 2007). This shows that even studies using the same n-back task with similar study parameters will still produce mixed results. Therefore, more research like the present study are needed to directly compare the results.

Another reason for not finding any difference in the n-back performance could be linked to the lack of changes in the depression scores. A past review study have shown that the cognitive impairments found in depressed patients are caused by or directly affected by the depressive symptoms the patients are currently experiencing (Hoy & Fitzgerald, 2010). Therefore, if there is no improvement in the depressive symptoms than there will also be no significant changes in terms of cognition. This relationship could explain the lack of changes on the n-back, since there were no significant improvements in the depression scores.

4.3 Brain Connectivity Changes

There are brain connectivity changes during the resting state, 0-back and 2-back conditions of the fMRI when comparing Time 1 and Time 2 scans. During the resting-state scans there was an increase in connectivity between the left frontal pole and the lateral occipital cortex and a decrease in connectivity with the middle temporal gyrus. There was also an increase in

connectivity between the right frontal pole and the bilateral lingual gyrus. During the 0-back condition, there was an increase in connectivity between the right hippocampus and the left caudate. Finally, during the 2-back condition, there was an decrease in connectivity between the right inferior frontal gyrus and right frontal pole. Also, an increase in connectivity between the left inferior frontal gyrus and right superior frontal gyrus.

4.3.1 Resting State

For the resting state scans, participants were instructed to stay awake and not to focus on anything. Although participants are not actively completing a task, it is still very important to look at brain connectivity differences during this phase. Past studies have shown significant activation and connectivity differences between healthy controls and depressed patients during resting state (Greicius et al., 2007; Veer et al., 2010; Zhu et al., 2012). Therefore, resting state differences offers researchers insights into the fundamental effects of depression on the brain.

Two of the three changes after the iTBS treatment were an increase in connectivity between the frontal poles and the lateral occipital cortex and the bilateral lingual gyrus. There are three possible explanations that are interconnected for this finding. First one relates to iTBS's potential to induce long term potentiation (LTP) in areas that were directly stimulated and the connecting areas (Huang et al., 2005, 2007). LTP in brain regions can already be seen after one stimulation, therefore studies have suggested that it may be more robust under repetitive treatment (Huang et al., 2005, 2007). In this study, the directly stimulated areas are the bilateral dorsolateral prefrontal cortex, which are connected to the frontal poles that showed significant changes after iTBS treatment. Therefore, the frontal poles of these participants could have experienced increased plasticity after the 25 days of iTBS due to its connection with the DLPFC. The two areas that showed increased connectivity with the frontal poles are the lateral occipital

cortex and the bilateral lingual gyrus, which are both relevant to the n-back task used in this study. The lateral occipital cortex and the lingual gyrus are involved in visual memory, visual attention and processing of visual information (Kozlovskiy et al., 2014; Pantazatos et al., 2012; Vogel & Machizawa, 2004). Activation of the lingual gyrus has been shown during visual tasks in the scanner, and during recollection of the task several weeks later (Machielsen et al., 2000). This finding is especially relevant to our study, as all participants practice the n-back task right before the resting state scan; thus, allowing them to recall the task during the resting state, thereby activating of the lingual gyrus. Past study has also found an increase in connectivity between the vmPFC (structure in the frontal pole) and the lateral occipital during visual tasks (Pantazatos et al., 2012). Therefore, we suggest that the increase in connectivity between the frontal poles and the bilateral lingual gyrus and the lateral occipital cortex during resting state is a result of the increased LTP of frontal poles in the context of the n-back task. The iTBS treatment may have strengthened the relevant connections needed to complete the n-back task through increased activation of the frontal poles during rest, which are known to be hypoactive in depression (Henriques & Davidson, 1991).

The second explanations relate to the idea of neural noise increasing or facilitating performance during rest, even when participants are not doing the task. Past study has found that brain stimulation treatment like TMS can induce neural activity in connected brain areas that provides a synergetic effect to the neural activity relevant to a task (Harris, Clifford & Miniussi, 2008). More specifically, the stimulation allows a disruption in the disturbed functional connections usually found in the brain of depressed patients, and help to organize it in a more constructive manner (Miniussi et atl, 2010). Applying this mechanism to our results suggest that the increased connectivity is a product of organized neural noise that will improve the efficiency

of the participants in the upcoming n-back task. Furthermore, the LTP explanation and the neural noise theory are not mutually exclusive, they may even be additive. The iTBS treatment may have increased the LTP of the frontal poles allowing it to form and strengthen beneficial connections during that are relevant, thus increasing the n-back task efficiency.

The last connectivity change is a decrease between the frontal pole and the middle temporal gyrus (MTG). Ma et al., (2012) found a reduced middle temporal gyrus volume in both the patients with treatment responsive depression and treatment resistant depression compared to healthy controls. Peng et al. (2011) have also reported reduced gray matter volume in the MTG in a group of individuals with first episode MDD. The frontal poles belong to the default mode network (DMN), which exhibits high levels of activity during resting state and play a critical role in the neurophysiological processes of episodic memory, self-reflective and emotional regulation (Greicius et al., 2007). Zhang et al. (2011) found MDD-related increases in nodal centralities within the DMN regions. In another study, Zhu et al. (2012) reported increased functional connectivity (FC) in anterior medial regions of the resting-state DMN is associated with rumination, whereas decreased FC in posterior medial regions which associated with over general autobiographical memory, suggesting that abnormal DMN activity might be an MDD trait. Therefore, the decreased connectivity between the frontal pole and the MTG could mean an improvement in the rumination symptoms, since the frontal pole is in the anterior medial region of the DMN. However, the decreased FC could also mean a disturbed relationship between the DMN and the MTG; the specific affect of this disturbed relationship very hard to determine since MDD is characterized by a plethora of symptoms (Greicius et al., 2007). Also, it is hard to determine whether there is excitatory effect or inhibitory effect from a functional connection in

MRI; thus, more research is needed to study this connectivity change in the context of depression.

4.3.2 0-Back

For the 0-back condition, participants are only required to press the number that respond to the number they see on the screen, so the WM is not involved during this condition. There was an increase in connectivity between the right hippocampus and the left caudate. The seed was placed in the hippocampus because it is related to spatial memory (Burgess, Maguire & O'Keefe, 2002), which is a part of the 0-back condition. The activation of the left caudate is expected because past studies have shown that it is involved in cognitive, and emotional processes (Ma et al., 2012; Shah et al., 2002). Structurally speaking, Shah et al. (2002) showed that TRD patients had less caudate gray matter volume than recovered patients and healthy controls, suggesting that the structure deficits of caudate might lead to some clinical symptoms observed in MDD. Ma et al., (2012) also found that the caudate had altered functional connection to widely distributed areas in the prefrontal regions, which may contribute to disturbances in mood and cognition in MDD patients. A past study using a spatial navigation task found that the hippocampus compensates for the caudate nucleus dysfunction with increased activity needed to maintain normal behavior (Voermanns et al., 2004). Thus, the increased connectivity found after the iTBS treatment in our study could suggest a cooperative interaction between the two areas, with the hippocampus compensating for the deficit in the caudate. Even though the 0-back condition does not elicit WM, it still requires cognitive functions like recognition, attention and recall, which are relevant to the hippocampus and caudate.

4.3.3 2-Back

During the 2-back condition the participants are tested on their WM, therefore several key cognitive functions are involved to accomplish the task. Interestingly, the areas showing connectivity differences are part of the cognitive control network, which includes brain regions responsible for multiple higher level cognitive functions (Cocchi et al., 2013). The cognitive control network is linked to WM because functions like executive functioning, inhibitions, and attention are part of both (Miyake et al., 2010; Niendam et al., 2012). The significant areas in this study like the frontal poles and inferior frontal gyri are part of the cognitive control network. The first connectivity change is between the right inferior frontal gyrus and the right frontal pole, where there is an decrease in the connectivity after the iTBS treatment. It is not surprising that both areas were activated during the 2-back, since past research have shown that both areas are involved in the high level cognitive functions needed to accomplish the WM task (Miyake et al., 2010; Niendam et al., 2012). The direction of the connectivity indicates an increase in efficiency when completing the 2-back task. A past fMRI n-back research has concluded that a decrease in the coupling means less resources are needed to perform at the same level as before (Bilek et al., 2011). Although we did not find any changes on the performance of the n-back task, the iTBS treatment may have resulted in an improvement in efficiency in the depressed patients. The mismatch between the performance scores and the brain activity changes could also be due to the dissociation between behavioural measures and brain mechanism. Miniussi et al. (2010) suggest that behavioural effects cannot translate directly to neural mechanism; therefore, it is important to discuss these findings separately.

The last connectivity change is an increase between the left inferior frontal gyrus and the right superior frontal gyrus. Both areas belong to the control cognitive network (Miyake et al.,

2010; Niendam et al., 2012), therefore the increase in functional coupling between them may suggest an improvement in cognitive control after iTBS treatment. The inferior frontal gyrus has been implicated in a classic inhibition task, the go/no go task (Aron, Robbins & Poldrack, 2004). The same area is also implicated in risk aversion, and past studies have shown TMS leads to change in risk attitudes and increased inhibition (Fecteau et al., 2007; Knoch et al., 2006). Inhibition is important during the 2-back condition because participants must restrict themselves from pressing the number on the screen at the present trial and instead report the number that was shown two trials ago. The superior frontal gyrus has been shown to be affected by depression (Taylor et al., 2004). Decreased activation of the superior frontal gyrus was found in depressed patients (Fitzgerald et al., 2008). Therefore, the increased coupling after the iTBS treatment may suggest a beneficial increased cognitive control of the superior frontal gyrus by the left inferior frontal gyrus during the WM task.

4.4 Limitations

A limitation involving the sample of this study is average age. The average age of the sample is 48.4 with 80% of the participants above the age of 40 years old. This creates a homogenous sample, which could reduce the generalizability of this study to other depressed age groups. Since age does affect cognition (Rao et al., 2015), the brain connectivity changes found in this study may only be applicable to a chronically depressed middle age population. Recently depressed patients or patients who do not have treatment resistant depression, may respond differently to the iTBS treatment, thus performing differently on the n-back task. Also, children or adolescence with depression may show no deficits on the n-back task compared to controls, therefore they may not show any brain connectivity changes induced by iTBS. Future studies should compare the effects of iTBS on WM across age groups and different on-set of diagnosis.

Another limitation in this study is the singular task used to measure working memory. The n-back task is a well-established measure of working memory, especially regarding fMRI studies looking at depression (Kane et al., 2007; Owen et al., 2005). However, same participant may perform different on different WM tasks (Jaeggi et al., 2010). Since, WM involves multiple cognitive modalities, WM tasks with different parameters could trigger different functions (Kane et al., 2007, Owen et al., 2005). Therefore, due to the nature of the n-back task, it may only be measuring one form of WM. Thus, the effects found in this study of iTBS on WM may not be replicable and comparable to other studies using different WM tasks.

One methodological limitation to this study is the sample size. This is because we encountered significant difficulties in participant recruitment, despite having recruited for almost two years. Only a small number of patients are prescribed iTBS treatment every month, and our study protocol limits the selection to first time iTBS patients with no changes in medication for at least four weeks. This results in a pool of approximately 1-3 patients per month, which greatly restricts the number of potential participants in our study. Also, some participants were unable to complete the second visit due to multiple reasons, resulting in a moderate drop out rate.

4.5 Future Directions

One methodological change future studies should consider is using multiple working memory tasks, specifically variations in terms of spatial versus non-spatial and verbal versus visual variations of WM tasks. It would be interesting to see if iTBS treatment will affect performances on these tasks differently since these tasks elicit different brain activations (Stipacek et al., 2003). Also, the n-back task has been shown to have mixed correlations with other WM tasks (Kane et al., 2007); therefore, using multiple WM tasks will allow future studies

to compare the effects of iTBS on these tasks, and capture a holistic view of the effects of iTBS on WM.

Past studies have shown that different parameters for the iTBS treatment could result in different clinical outcomes (Preston et al., 2010); thus, future studies could compare effects of different iTBS protocols on WM. The stimulation protocol, treatment duration and the stimulation site(s) are all possible variations that could be studied. Studies have suggested that receiving brain stimulation right before the n-back task may induce greater changes in brain activation (Preston et al., 2010). Therefore, future studies could look into the effects of iTBS stimulation at different intervals before WM tasks.

Futures studies could also build on this pilot study by adopting a randomized, sham-controlled, double-blind design to obtain definitive results on the effects of iTBS on WM. It would be interesting to see if the iTBS treatment is better than sham in inducing changes in WM. Also, a matched control group should be used to see the performance and brain activity of the depressed patients are able to reach control participants' level after iTBS treatment.

4.6 Conclusion

The results in this pilot study suggest that 25 days of left and right dorsolateral prefrontal cortex iTBS treatment may result in changes in connectivity between certain brain areas during a working memory task. The connectivity changes suggest possible increased efficiency, beneficial reorganization and increased cognitive control during the n-back after the treatment. There were no improvements for the accuracy and reaction time on the n-back task and the depression scores before and after treatment. This could be due to the iTBS protocol used or the characteristic of the sample used in this study. Further research is needed to determine if different stimulation sites and parameters may be able to produce therapeutic changes in WM in depressed patients.

Plus, additional WM tasks should be used to capture a complete picture of the possible effects of iTBS on WM. This study has provided insight into some of the brain activation changes involved in WM for depressed patients, and outlined a number of ways to improve future studies. Overall, more research is needed to understand the therapeutic potential of a second line depression treatments like iTBS, for both mood and cognitive deficits in depression.

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