A Randomized Double-Blind Sham-Controlled Comparison of Unilateral and Bilateral Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Major Depression

By

Daniel Michael Blumberger

A thesis submitted in conformity with the requirements for the degree of Masters of Science
Institute of Medical Science
University of Toronto

© Copyright by Daniel M. Blumberger 2011
Abstract

Objectives: High frequency left-sided (HFL) and low frequency right-sided (LFR) unilateral repetitive transcranial magnetic stimulation (rTMS) are efficacious in treatment-resistant major depression (TRD). Similar benefit has been suggested for sequential bilateral rTMS (LFR then HFL). Therefore, this study evaluated the efficacy of HFL and sequential bilateral rTMS compared to sham in TRD.

Methods: Seventy-four subjects between the ages of 18 and 85 with TRD and a 17-item Hamilton Depression Rating Scale (HDRS) greater than 21 were randomized to receive unilateral, bilateral, or sham rTMS. Remission rates were compared among the three groups.

Results: Remission rates differed significantly among the three groups. The remission rate was significantly higher in the bilateral group (34.6%) than the unilateral (4.5%) and sham (5.0%) groups. The remission rate in the unilateral group did not differ from sham group.

Conclusion: These findings warrant larger controlled studies that compare the efficacy of sequential bilateral rTMS and HFL rTMS in TRD.
Acknowledgments

A CAMH Postdoctoral Fellowship Award and a Canadian Institutes of Health Research Postdoctoral Fellowship Award supported me in this work.

I would like to thank the following people for their invaluable advice and input into the work represented by this thesis.

**Thesis Supervisor:** Z. Jeff Daskalakis MD, PhD, FRCPC

**Fellowship Supervisor:** Benoit H. Mulsant MD, MS, FRCPC

**Thesis Committee Members:** Arun Ravindran, MD, PhD, FRCPC

Robert Chen, MD, PhD, FRCPC

**Statistical Consultant:** Tamara Arenovich, MSc
# Table of Contents

Title Page ................................................................................................................. i

Abstract ..................................................................................................................... ii

Acknowledgments ...................................................................................................... iii

Table of Contents ...................................................................................................... iv

List of Tables ............................................................................................................. vii

List of Figures ........................................................................................................... viii

Chapter 1 Overview, Goals and Study Objectives ..................................................... 1

1 Overview ............................................................................................................. 1

2 Goals of the Current Study .................................................................................... 2

  2.1 Specific Objectives ......................................................................................... 2

  2.2 Specific Hypotheses ....................................................................................... 3

Chapter 2 Background .............................................................................................. 4

  3 Background ..................................................................................................... 4

    3.1 Major Depression .......................................................................................... 5

    3.2 The Definition of Treatment-Resistant Major Depression ......................... 6

    3.3 Epidemiology and Impact of Treatment-Resistant Major Depression in Adults .... 7

    3.4 Epidemiology and Impact of Treatment-Resistant Depression in Late-Life .......... 8

    3.5 Impact of Treatment-Resistant Depression in Late-Life and the Need for Alternative Treatments 9

Chapter 3 Repetitive Transcranial Magnetic Stimulation ......................................... 11

  4 Repetitive Transcranial Magnetic Stimulation ..................................................... 11

    4.1 Repetitive Transcranial Magnetic Stimulation in Major Depression ............ 13

        4.1.1 Repetitive Transcranial Magnetic Stimulation in Major Depression: Early Studies .......... 14

        4.1.2 Repetitive Transcranial Magnetic Stimulation in Major Depression: Later Studies .......... 16

        4.1.3 Repetitive Transcranial Magnetic Stimulation in Major Depression: Bilateral Parameter Configurations ............................................................................................................. 18

        4.1.4 Meta-Analyses of Repetitive Transcranial Magnetic Stimulation in Major Depression .......... 21

    4.2 Rationale for Further Investigation of Bilateral rTMS ................................... 25
List of Tables

Table 1 Inclusion and Exclusion Criteria.................................................................................. 36
Table 2 Treatment Parameters .................................................................................................. 37
Table 3 Demographic and Baseline Clinical Characteristics.................................................... 45
Table 4 Remitters By Age.......................................................................................................... 47
Table 5 Mean HDRS scores (SD) by week ................................................................................. 48
Table 6 Cognitive Change Scores.............................................................................................. 49
Table 7 Cognitive Change Scores and Remission Status.......................................................... 50
Table 8 Dropouts By Age ......................................................................................................... 51
List of Figures

Figure 1. DSM-IV Criteria for a Major Depressive Episode .......................................................... 28
Figure 2. Thase and Rush Staging of Treatment-Resistant Depression................................. 29
Figure 3. CONSORT Flow Diagram ......................................................................................... 52
Figure 4. Mean HDRS Change Scores ...................................................................................... 53
Figure 5. Intensity of Magnetic Field as a Function of Distance from the Coil ......................... 68
Chapter 1
Overview, Goals and Study Objectives

The purpose of this chapter is to:

1. Provide an overview of the rationale for this thesis project
2. Introduce the goals of the project and study objectives

1 Overview

Major depressive disorder is a highly prevalent illness. Despite a vast number of pharmacological options, a significant percentage of patients fail to respond to first line treatments. In addition, a significant proportion of those suffering from depression are not able to tolerate multiple separate antidepressants. Persistent depression exacts a devastating toll on individuals through a variety of different mechanisms: worse medical outcomes, increased disability, higher rates of mortality from medical illnesses and suicide, increased caregiver burden and overall reduced quality of life. Alternative treatments are needed to reduce the burden of depression on patients, families and society. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation treatment that has shown promise as a potential alternative treatment for depression that does not respond to pharmacotherapy. There are few side effects from this treatment and it involves a different mechanism of action then
pharmacological treatment. However, the optimal method of stimulating to improve depression has not been clarified. Therefore, this study sought to examine the efficacy of two of the most promising forms of rTMS in treatment resistant depression (TRD), under randomized controlled conditions.

2 Goals of the Current Study

The vast majority of rTMS studies in depression have examined high frequency left-sided (HFL) stimulation of the dorsolateral prefrontal cortex (DLPFC). In some respects it has become the standard form of stimulation in depression treatment trials. A number of studies have also shown improvement in depression with low frequency right-sided (LFR) stimulation. The sequential combination of LFR immediately followed by HFL has shown higher response and remission rates than either HFL or LFR alone. Therefore, the present study was conducted to compare the efficacy of bilateral (sequential LFR and HFL) rTMS with unilateral (HFL) and sham rTMS for TRD.

2.1 Specific Objectives

1. To compare the efficacy of sequential bilateral rTMS, unilateral and sham rTMS.

2. To compare the safety and tolerability profile of sequential bilateral and sham rTMS.
2.2 Specific Hypotheses

1. Bilateral rTMS will show greater efficacy than unilateral and sham rTMS and unilateral rTMS will show greater efficacy than sham rTMS.

2. There will be no differences in the safety and tolerability profile among the three groups.
Chapter 2

Background

The purpose of this chapter is to:

1. Define depression and review its significance

2. Review the epidemiology and impact of treatment resistant depression across the lifespan.

3. Provide an overview of rTMS and the findings in previous depression trials.

4. Review the rationale for investigating the two types of rTMS parameters used in this study.

3 Background

Depression will be the leading cause of disease burden in the next 25 years. High rates of treatment resistance in both younger and older adults warrant the investigation of novel treatments for this illness. Repetitive TMS is a potential novel treatment for TRD. Since the first published studies showing that rTMS was effective at improving mood for patients with MDD (George et al. 1996; Pascual-Leone et al. 1996) there have been over 85 published studies evaluating the efficacy of rTMS for TRD (Daskalakis et al. 2008; Slotema et al. 2010). Several meta-analyses have found moderate (Martin et al. 2003) to large effect sizes (Burt et al. 2002; Gross et al. 2007; Holtzheimer et al. 2001; Kozel and George 2002; Schutter 2009; 2010;
Slotema et al. 2010) based on differing inclusion criteria. A more recent meta-analysis has demonstrated that later studies had a larger weighted mean effect size (0.76) than the earlier studies included in a previous meta-analysis (0.35) (Gross et al. 2007). The authors proposed that their result reflects ongoing refinement and improvement in stimulation parameters over time (Gross et al. 2007). In spite of such observations, there is little consensus on the optimal methods of stimulation for patients with TRD.

3.1 Major Depression

Major depression is the most important of the depressive disorders. In North America, the most common method of diagnosing a Major Depression is the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (2000). A major depressive episode lasts a minimum of two weeks and is characterized by a predominantly depressed mood the majority of most days and/or significantly diminished interest or ability to take pleasure in most activities the majority of most days. In addition, five or more symptoms presented in Figure 1 must be present and prominent the majority of the two weeks. In addition the symptoms cannot be accounted for the use or withdrawal of substance or the direct consequence of a general medical condition. Furthermore the symptoms must cause a significant degree of functional impairment whether social or occupational. A major depression cannot be diagnosed in the context of bereavement (i.e. within the first two months of loss of a loved one). After an individual has experienced one major depressive episode they have a Major Depressive Disorder (MDD). MDD is one of the most prevalent mental illnesses (Kessler et al. 2003; Patten et al. 2006). It is an illness associated with significant morbidity that leads to substantial disability, reduced quality of life, medical complications and mortality from suicide (Greden 2001b; Penninx et al. 2001; Ustun et
al. 2004). It is estimated that by the year 2030, depression will be the leading cause of disease burden (World Health Organization. 2009). Depression is one of the leading causes of disability worldwide (Greden 2001a; Lopez et al. 2006; McKenna et al. 2005; Murray and Lopez 1997; Ustun et al. 2004). The first-line treatment of a major depressive episode can involve the use of pharmacotherapy, psychotherapy or a combination of the two. However, access to evidence-based psychotherapies is limited and patients are more frequently given a trial of a selective serotonin reuptake inhibitor (SSRI) as an initial treatment (Lam et al. 2009). In general, this medication class is associated with reasonable tolerability however, side effects can include: drowsiness, sedation, insomnia, headache, dry mouth, blurry vision, diaphoresis, dizziness, hypertension, nausea, vomiting, constipation and gastrointestinal upset. In addition, sexual dysfunction in men and decreased libido in women have been reported in 50% of patients and can affect quality of life and adherence to medication (Taylor et al. 2005).

3.2 The Definition of Treatment-Resistant Major Depression

Treatment-resistant depression (TRD) has been defined as failure to achieve remission with one or two adequate antidepressant medication trials (Berlim and Turecki 2007; Fava 2003; Kornstein and Schneider 2001). The adequacy of a treatment trial of medication can be measured based on the dose, duration at maximal dose, adherence and clinical outcome using the antidepressant treatment history form (ATHF) (Oquendo et al. 2003; Sackeim 2001). This method of assessing adequacy of prior treatment is reliable and can be used to predict treatment response to medication and ECT (Tew et al. 2006). The degree of treatment resistance can also be described based on stages. Several groups have outlined various methods and criteria for categorizing and staging treatment resistance. Thase et al. (1995) devised a hierarchy of
treatments (see Figure 2) that aid in clarifying the degree of treatment resistance (Thase and Rush 1995). However, this staging method does not clearly define the adequacy of treatment trials. The Massachusetts General Staging Method uses scoring of the type and intensity of treatment to come up with a continuous measure of treatment resistance (Petersen et al. 2005). The Maudsley staging method goes one step further and includes depressive symptom duration and severity along with type and intensity of treatment to come up with a score between 3 (mild) and 15 (severe) (Fekadu et al. 2009).

3.3 Epidemiology and Impact of Treatment-Resistant Major Depression in Adults

Though a number of effective treatments are available for major depression, as many as 50% of patients fail to respond to treatment (Fava 2003; Pincus and Pettit 2001; Sackeim 2001). In addition, the switching, augmentation and combination strategies frequently used in TRD often increase the risk of adverse events and drug interactions (Dew et al. 2007; Joo et al. 2002; Papakostas 2008). Despite advancements in antidepressant treatments only a minority of patients achieve full remission of their symptoms after a single trial of antidepressant medication. In the large Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial close to a third of patients continued to experience persistent depressive symptoms despite 4 separate medication and/or augmentation trials (Fava et al. 2006; McGrath et al. 2006; Nierenberg et al. 2006; Rush et al. 2006b; Trivedi et al. 2006). In addition, 10-30 percent of patients will discontinue antidepressant medications due to adverse effects (Montgomery et al. 1994). The failure of first line treatment to induce remission in patients leads to impaired psychosocial function and
diminished quality of life (Blazer 2002; Doraiswamy et al. 2001; Keller 2003). The effects of resistant depression exacerbate and prolong the burden of depression on financial, social and health outcomes for both the individual and society (Greden 2001a).

3.4 Epidemiology and Impact of Treatment-Resistant Depression in Late-Life

Depression is the most common, treatable, mental disorder in late life, making it a major public health concern: 2 to 4 % of persons over the age of 65 suffer from major depression (Blazer 2003). Furthermore, by the year 2031, 25% of the population will be over 65 (Belanger et al. 2005). By these estimates, up to 360,000 adults over the age of 65 will suffer from major depressive disorder in Canada. The rates of clinically significant depressive syndromes in older adults have been reported to range from 11.5 to 30% (Blazer and Williams 1980; Copeland et al. 1992; Steffens et al. 2000). These data predict an epidemic of LLD that will place tremendous burden on the healthcare system. LLD is also typically complicated by co-morbid medical illness and polypharmacy and it is associated with higher rates of disability and mortality (both from suicide and physical illness)(Ganguli et al. 2002; Lenze et al. 2001; Rovner et al. 1991). Older adults with depression who suffer a myocardial infarction are four times more likely to die within 4 months than those without depression (Romanelli et al. 2002) and the risk of a suicide attempt is double in the elderly compared to younger adults (Minino et al. 2002). As a result, LLD is associated with higher rates of healthcare utilization and hospitalization (Huang et al. 2000; Katon et al. 2003; Unutzer et al. 2006). Current pharmacological treatments for LLD, however, provide modest efficacy. It is estimated that close to 40% of patients are resistant to
antidepressants (Mulsant et al. 2006; Mulsant and Pollock 1998; Whyte et al. 2004b). Further, the elderly are more likely to experience relapses and recurrences than younger adults (Mulsant et al. 2006; Reynolds et al. 2006; Tew et al. 2006). Rates of treatment resistance in randomized controlled trials in LLD are as high as 77% using an SSRI (Allard et al. 2004) and range from 55-81% using serotonin/norepinephrine reuptake inhibitors (SNRI) (Allard et al. 2004; Kok et al. 2007; Raskin et al. 2007; Schatzberg and Roose 2006). Antidepressant augmentation strategies (e.g., addition of lithium or antipsychotics) are problematic insofar as the elderly have increased sensitivity to adverse effects (Dew et al. 2007) such as falls (Joo et al. 2002).

3.5 Impact of Treatment-Resistant Depression in Late-Life and the Need for Alternative Treatments

To date, few well-tolerated treatments are available for TRD in adults and in later-life. Medication strategies include switching to another medication within the same class, switching to another medication in a different class, augmentation of the current antidepressant with another medication, augmentation with psychotherapy or a trial of electroconvulsive therapy (Kennedy et al. 2009; Lam et al. 2009; Parikh et al. 2009) The remission rates with the psychopharmacological methods and psychotherapy were modest (between 14 and 30% depending on degree of treatment resistance) in the STAR*D trial (Rush et al. 2006a; Rush et al. 2006b; Trivedi et al. 2006). Only a small number of elderly subjects were included in this trial. Therefore, there is a limited ability to the generalize this data to older depressed patients. In one of few published placebo-controlled pharmacotherapy trials for TRLLD, Sunderland et al. (1994) found that the monoamine oxidase inhibitor (MAOI) selegiline was efficacious (Sunderland et al.
1994). However, a more recent randomized comparison of lithium augmentation and the monamine oxidase inhibitory phenelzine for TRLLD found one-third of those receiving lithium remitted versus none receiving phenelzine (Kok et al. 2007). These two controlled studies suffer from small sample size, short duration, and inclusion of subjects with very severe symptoms. Thus, there appears to be minimal controlled data to inform the treatment of treatment-resistance in LLD. There are a number of preliminary open-label studies that have examined treatment strategies for TRLLD: studies of switching from an SSRI to nortriptyline (Houck et al. 2003), venlafaxine (Whyte et al. 2004a), and duloxetine (Karp et al. 2008), a stepwise strategy of bupropion, nortriptyline, or lithium augmentation of SSRI (Dew et al. 2007; Mulsant et al. 2001), and ECT (Dombrovski et al. 2005; Tew et al. 1999). A significant proportion (40-50%) of SSRI nonresponders responded to these strategies. However, many patients did not respond or tolerate these strategies and significant percentage relapsed very quickly (Dombrovski et al. 2007; Reynolds et al. 2006).

The primary indication for ECT is TRD. ECT can be effective in up to 65 percent of patients with TRD (Kellner et al. 2010; Sackeim et al. 2009). The most effective treatment for treatment-resistant LLD is ECT where remission rates range from 55 to 90% (Flint and Gagnon 2002; Greenberg and Kellner 2005). However, many patients often refuse to accept a trial of ECT due to fear, social stigma and the risk of cognitive side effects (Lisanby 2007; Sackeim et al. 2007). The anterograde and retrograde memory impairments following a course of ECT can persist for up to 6 months (Sackeim et al. 2007). The cognitive effects of ECT can be severe and patients are often unable to work for months after having a course of treatment (Lisanby et al. 2000; Prudic et al. 2000). Furthermore, advancing age is a risk factor more significant cognitive side effects (Sackeim et al. 2007). Thus, the need for alternative treatment strategies to optimize
outcomes for patients who experience TRD has been recognized as one of the future directions for addressing this disorder (Insel 2006).

4 Repetitive Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a unique experimental technology that allows researchers to non-invasively study the brain in healthy and diseased states (Barker et al. 1985). It has been used as an investigational tool to measure phenomena such as cortical inhibition and plasticity (Classen et al. 1998; Kujirai et al. 1993) and as a probe to explore cognitive mechanisms (Flitman et al. 1998). Furthermore, it has been investigated as a treatment modality in various neuropsychiatric disorders such as depression and schizophrenia (Hoffman et al. 2000; Pascual-Leone et al. 1996).

In 1831 Michael Faraday demonstrated that a current could be induced in a secondary circuit when it was brought in close proximity to the primary circuit in which a time-varying current was flowing. In keeping with Faraday’s law a changing electrical field produces a changing magnetic field that causes current to flow in a nearby conducting material. With a TMS device an electrical charge is stored in a capacitor and periodic discharge of stored energy from the capacitor and through the conducting coil produces a time-varying electrical field. The electrical field will produce a transient magnetic field that causes current to flow in a secondary conducting material, such as neurons. The discharge from a TMS coil over the scalp induces a depolarisation of the underlying neural tissue. The magnetic field produced by the coil penetrates largely unimpeded, as the underlying scalp and skull are non-conducting tissues. The orientation and intensity of the current travelling through the coil determines the type of tissue
stimulated as well as strength of that stimulation. The standard figure-of-eight coils used in
rTMS depression trials activate neurons in a cortical area of approximately 3 cm$^2$ and to a depth
of approximately 2 - 3cm (Barker 1999). The generally accepted positioning for a figure-of-eight
coil is held over the scalp flat, at about 45º from the midline position, perpendicular to the central
sulcus. This positioning induces a current from anterior to posterior, perpendicular to descending
pyramidal neurons and parallel to interneurons. Interneurons are important cells that have the
ability to modulate pyramidal cell firing (Amassian and Deletis 1999). The orientation between
the coil and underlying neural tissue allows researchers to selectively activate different groups of
neurons. This ability to selectively activate different groups of neurons is essential to
understanding the principles that mediate therapeutic efficacy. By virtue of the fact that TMS
activates neurons trans-synaptically (Rothwell 1997) (i.e., activation of interneurons), neuronal
stimulation can selectively activate or inhibit the cortex. The ability to selectively activate or
inhibit the cortex may be involved in the treatment effects when applied to the cortex.

Repetitive TMS involves the stimulation of the brain by a train of magnetic pulses at
frequencies between 1 to 50 Hz (Wassermann et al. 1998). It has been shown to be an effective
therapeutic tool for the treatment of depression (Fitzgerald et al. 2003; George et al. 1995;
Pascual-Leone et al. 1996). The first studies published demonstrating efficacy of rTMS for
depression were reported in the mid 1990’s. These studies produced promising results with
reduced depression severity following dorsolateral prefrontal cortex (DLPFC) stimulation
(George et al. 1995; Pascual-Leone et al. 1996).

The DLPFC is a brain region that is highly interconnected with the “affective circuit”.
This circuit involves various other deeper neuroanatomical structures (Nestler et al. 2002;
Vaidya and Duman 2001). The affective circuit is comprised of the connections of the ventral
and anterior division of the anterior cingulate cortex including the hypothalamus, amygdala,
orbitofrontal cortex, nucleus accumbens, and other limbic structures (Drevets et al. 2008; Mayberg et al. 1999; Ongur et al. 2003). Other imaging studies have demonstrated that MDD involves dysregulation of cortical activity with lower activity in the left DLPFC and higher activity in the right DLPFC (Baxter et al. 1989; Fitzgerald et al. 2008).

Functional neuroimaging data has demonstrated that rTMS can improve DLPFC dysfunction. Investigators have shown that targeting the frequency of rTMS treatment to underlying DLPFC hyper or hypometabolism is related to treatment response (Drevets 2000a; 2000b; Kimbrell et al. 1999). That is, low frequency rTMS for a period of approximately 15 minutes induces a transient inhibition of the cortex, thus providing a mechanism to address the right-sided hyperfunction found in depression (Chen et al. 1997a). In contrast, high frequency stimulation has been shown to increase excitability, thus providing a therapeutic tool to address the left-sided dysregulation found in depression (Fitzgerald et al. 2006b; Pascual-Leone et al. 1994). These findings suggest that some of the therapeutic effects of rTMS may be coordinated through enhanced GABA mediated inhibitory neurotransmission and is consistent with studies that show GABAergic neurotransmission is disrupted in MDD (Levinson et al. 2010; Sanacora et al. 1999) and enhanced through either ECT or treatment with SSRI antidepressants (Sanacora et al. 2003; Sanacora et al. 2002).

4.1 Repetitive Transcranial Magnetic Stimulation in Major Depression

Since the first published studies showing that rTMS was effective at improving mood for patients with MDD (George et al. 1996; Pascual-Leone et al. 1996) there have been well over 85
published studies evaluating the efficacy of rTMS for treatment resistant MDD (TRD). The most relevant prior research will be summarized in four separate categories: (1) early studies, which evaluated the efficacy of 10 rTMS sessions (i.e., 2 weeks) for TRD; (2) later studies, which evaluated the efficacy of rTMS for more than 10 rTMS sessions; (3) novel studies, which evaluate the efficacy of rTMS using various non-conventional treatment approaches (i.e. bilateral rTMS); (4) meta-analyses of rTMS for TRD.

4.1.1 Repetitive Transcranial Magnetic Stimulation in Major Depression: Early Studies

Repetitive TMS studies applied at high frequencies (10-20 Hz) over the left prefrontal cortex has demonstrated efficacy in the treatment of depression. George et al.(George et al. 1995) initially reported modest improvement (mean Hamilton Depression Rating Scale (HDRS) Score decreased from 23.8 to 17.5) in 6 treatment-refractory depressed patients in an open study using rTMS. Very promising results were also reported by Pascual-Leone et al.(Pascual-Leone et al. 1996) who showed rTMS was effective at treating depressive symptoms in 17 patients with medication-resistant depression with psychotic features when applied daily for 1 week. This was a multiple crossover, randomized placebo-controlled study with sham rTMS and stimulation of different cortical areas used as control conditions. Similarly, George et al.(George et al. 1997) and Figiel et al.(Figiel et al. 1998) reported significant improvement in depressive symptoms in a group of patients with major depression in 2-week placebo-controlled crossover trials of real and sham high frequency rTMS. Grunhaus et al.(Grunhaus et al. 2000) also compared rTMS to ECT in 40 patients with MDD. They found that rTMS was less effective than ECT in patients with MDD and psychosis, but was equal to ECT in patients without psychosis.
Several studies have also demonstrated LFR rTMS administered to the DLPFC to be effective in depression. For example, in a large double blind study of 70 depressed patients Klein et al. (Klein et al. 1999) examined the therapeutic efficacy of prefrontal LFR rTMS. Patients were randomly assigned to receive rTMS or sham rTMS. After 2 weeks of treatment 49% of rTMS treated patients were classified as responders (i.e. >50% reduction in HDRS Score) whereas only 25% of patients treated with sham rTMS responded. Other studies have also demonstrated LFR rTMS to be useful in depression (Feinsod et al. 1998; Geller et al. 1997; Menkes et al. 1999).

Other early rTMS trials in depression have been equivocal or shown lack of efficacy. For example, Berman et al. (Berman et al. 2000) reported only a modest reduction in depressive symptoms following a 10-day course of high frequency rTMS to the left prefrontal cortex. This study was conducted in a double-blind placebo (i.e. sham) controlled manner. Similarly, Loo et al. (Loo et al. 1999) failed to find a significant difference between real and sham high frequency rTMS to the left prefrontal cortex in 18 patients with depression following 2 weeks of treatment. Other studies have also reported negligible results (Hoflich et al. 1993; Padberg et al. 1999). Several explanations may account for these discrepant findings. First, the studies included varying inclusion criteria ranging from moderate to severe TRD and may represent a relatively heterogeneous subset of patients whose underlying disorder may be confounded by other comorbidities. Second, stimulation parameters including frequency, intensity and duration vary from study to study, precluding the proper determination of these parameters to optimize the therapeutic response. Third, the lack of control around concomitant use of medications in these studies introduces a source of potential bias on the independent effects of rTMS on mood symptoms making it unclear whether improvement was related to rTMS alone, medication or the combination of both. Fourth, no consistent method for precisely localizing the prefrontal cortex
has been devised and, as such, different cortical areas may be stimulated between subjects and between studies confounding treatment results. Collectively these studies provided promising evidence that rTMS represented a potential new treatment modality for depression. However, as the treatment effects were typically of modest therapeutic efficacy additional studies with enhanced treatment parameters were investigated.

4.1.2 Repetitive Transcranial Magnetic Stimulation in Major Depression: Later Studies

The majority of early rTMS studies involved treatment durations that were typically 2 weeks in duration. The rationale for increasing treatment duration relates to the efficacy of ECT in TRD where a typical treatment course last three to six weeks in the acute phase. In this regard, later studies have been completed or are currently underway utilizing 20 or more treatments to optimize clinical efficacy. Fitzgerald et al. (Fitzgerald et al. 2003) randomized 60 patients to either high frequency (i.e., 10 Hz) rTMS to the left DLPFC (HFL) or low frequency (i.e., 1 Hz) rTMS to the right DLPFC (LFR) or a sham stimulation condition (n=20 in each group). All had TRD and had failed multiple antidepressant medication trials (mean number = 5.7 ± 3.4). There were no baseline clinical or demographic differences between the three groups. Over the double blind phase of the study there was clearly an antidepressant effect of both active groups that was superior to the response to sham stimulation. There was also continued improvement in both active groups across the 4 weeks of the study: after the 4 weeks of treatment the mean percentage change in MADRS score from baseline was 48.0 ± 17.9% (range 15.1 – 87.5%). These results demonstrate that both HFL TMS and LFR TMS have substantial therapeutic efficacy and that clinical response appeared to require at least 20 sessions (four
weeks) of treatment with the parameters used. Avery et al. (Avery et al. 2006) compared 3-weeks of HFL rTMS to sham rTMS in 68 patients with TRD and demonstrated that 30.6 percent of patients who received HFL rTMS met criteria for therapeutic response (i.e. greater than 50 percent decrease in symptoms on the HDRS-17). The results were statistically better than sham stimulation in which only 6.1 percent of subjects met criteria for therapeutic response. Furthermore, the remission rate for the HFL group was 20% (i.e., HDRS < 8) statistically superior compared to 3% in the sham group. One of the largest studies to date evaluating the efficacy of HFL rTMS compared to sham rTMS was conducted by a private TMS manufacturer (Neuronetics Ltd). This study was a randomized trial of HFL rTMS (10 Hz) compared to sham rTMS in 301 medication-free patients who had not benefited from prior antidepressant treatment (O'Reardon et al. 2007). The results of this study demonstrated that following 6-weeks of HFL rTMS there was a 6.3-point greater reduction in HDRS-24 scores relative to sham and only a 3.4-point difference relative to sham stimulation on the a priori primary outcome variable. Finally, 24 percent of patients receiving HFL rTMS met response criteria compared to 12 percent receiving sham. Recently an NIMH funded clinical trial involving four US sites compared up to 6-weeks of 10 Hz HFL rTMS to placebo in 199 unmedicated TRD patients between the ages of 22 and 69. This study demonstrated a statistically significant clinical effect in which 14% of patients receiving active treatment met criteria for response compared to only 5% sham treated patients (George et al. 2010) yielding a number needed to treat of 12. In an open-label extension phase of the study, whereby placebo non-responders were crossed over to active treatment 30% of subjects in this group achieved remission. In this study, remitters and responders were more likely to have a lower degree of treatment resistance. Older age was not associated with a lower likelihood of improvement, which likely reflects the optimized measures used in this study. The investigators optimized the intensity of the treatment to 120% for all subjects, used MRI imaging
to locate the DLPFC and allowed for up to 6 weeks of treatment. MRI imaging allowed for
determination of the DLPFC. If the location of the coil placement was too far posterior the coil
placement was moved 1 cm anterior prior to initiating treatment. In one third of the subjects the
coil placement was over the premotor area rather than the DLPFC. Extending the duration of
the active treatment phase by 3 more weeks led to more than double the number of subjects
achieving remission than in the first 3 weeks.

4.1.3 Repetitive Transcranial Magnetic Stimulation in Major Depression:
Bilateral Parameter Configurations

Several novel stimulation approaches have been investigated in an attempt to improve
rTMS treatment efficacy including bilateral rTMS. Such investigations were initiated, in part, as
a result of the evidence that bilateral ECT is superior to unilateral ECT at similar stimulus
parameters and from the evidence that both HFL rTMS and LFR rTMS result in an
antidepressant response (Fitzgerald et al. 2003). An initial attempt at applying simultaneous
bilateral high frequency rTMS was unsuccessful (Loo et al. 2003). Subsequently, there have
been a number of trials of sequential bilateral rTMS combining HFL rTMS and LFR rTMS. A
small case series with 4 patients out of 7 classified as responders to bilateral stimulation (Cohen
et al. 2003). A brief (5 day) treatment study comparing HFL rTMS to bilateral rTMS and a
condition with high (10Hz) and low (1Hz) frequency rTMS both applied to left DLPFC which
showed no difference between the groups (Conca et al. 2002). However, this study was of
relatively short duration (i.e., 5 consecutive days) and included a relatively small sample size
(i.e., n=12 per group). Thus the failure to show group differences was likely secondary to
exceptionally high response rates demonstrated by all treatment groups. This likely to reflect the lack of a sham control and the difficulty separating out the non-specific treatment factors. In another, slightly larger study, Hausmann et al. (Hausmann et al. 2004) compared sequential bilateral, HFL unilateral and sham rTMS in inpatients who were concomitantly initiated on antidepressant medication with rTMS. Thus, this study was a randomized-controlled comparison of bilateral, unilateral and sham rTMS combined with pharmacotherapy (Hausmann et al. 2004). The initiation of an antidepressant at the same time as rTMS likely confounded the findings given that antidepressant treatment effects are typically observed within 2-4 weeks. In addition, Hausmann et al. (Hausmann et al. 2004) used sequential active and sham stimulation in the same treatment session in the HFL subjects. This configuration likely compromised the blinding as some subjects would have been able to tell the difference between sham and active treatment, particularly at higher intensities. Rybak et al. (Rybak et al. 2005) examined the efficacy of bilateral rTMS and HFL rTMS in 18 subjects with TRD. This study showed no significant differences between active treatment groups but it was relatively underpowered to show between group differences. Two thirds of patients in the bilateral rTMS and 5/9 in the HFL rTMS group met response criteria. This high response rate may reflect the fact that this was not a sham-controlled trial. Another group of investigators examined the effect of two forms of sequential bilateral rTMS compared to a sham condition (McDonald et al. 2006). HFL was given first followed by LFR in one group and LFR was given first then followed by HFL in another group. There were no differences on the primary outcome of remission between the three conditions. The study was compromised by an imbalance in the amount of treatment resistance between the three groups and by a short treatment duration of only 2 weeks.

These studies, however, were limited in several important ways. First, bilateral rTMS was not compared to unilateral and sham rTMS in a sufficiently large sample of subjects (e.g. 50)
needed to minimize Type II error and stabilize statistical parameter estimates (Norman and Streiner 2000). Also, none of the aforementioned studies was conducted for longer than 10 days. A recent study compared LFR to sequential bilateral rTMS (Pallanti et al. 2010). In this study, 420 pulses of LFR were given at 110% intensity, while sequential bilateral treatment was given with 420 pulses LFR at 110% followed by 1000 pulses of HFL at 100% intensity. The sham condition consisted of sequential bilateral stimulation with the same number of pulses using a sham coil. There were no differences between the three groups on remission rates. The LFR group did show a higher rate of response. However, this study was still of relatively short duration (three weeks). Fitzgerald et al. (Fitzgerald et al. 2006a) used sequential bilateral rTMS (i.e., 1 Hz rTMS to the right DLPFC followed by 10 Hz rTMS to the left DLPFC) compared to sham stimulation in 50 patients with TRD (25 per group). Treatment was provided for up to 6 weeks, longer than any previously published rTMS trial at the time. In this study there was a marked benefit of bilateral rTMS over sham stimulation. There was a significant difference between the groups at 2 weeks ($F_{(1,25)} = 25.5, p<0.001$) which remained significant at all other trial time points ($F_{(5,44)} = 3.9, p=0.005$). Patients continued to respond across the 6 weeks of active treatment. Most importantly, at the completion of the study, 13 of 25 patients in the bilateral group (>50%) and only 2 in the sham group met response criteria on the HDRS. Thirty-six percent of patients in the bilateral group (9 of 25) and no patients in the sham group met criteria for remission. A further 45% of patients in the sham group who crossed over to bilateral treatment at trial end went on to respond in a manner meeting response criteria (33% remission criteria). These response and remission rates were higher than previous sham controlled rTMS trials and indicate a clinically relevant level of response, especially given that this was a highly treatment resistant sample of patients (mean number of unsuccessful antidepressant medication courses = $5.9 \pm 3.0$) with moderate to severe symptoms. These findings provided impetus to
further clarify the role of sequential bilateral compared to the conventional unilateral HFL rTMS in the treatment of patients with TRD

4.1.4 Meta-Analyses of Repetitive Transcranial Magnetic Stimulation in Major Depression

There have been more than ten meta-analyses evaluating the antidepressant effects of DLPFC rTMS. All but one have shown greater antidepressant effects of two weeks of high frequency left rTMS (HFL rTMS) compared to sham; these included an analysis of 6 reports (McNamara et al. 2001), of 12 studies (Holtzheimer et al. 2001) of 16 studies (Burt et al. 2002) of 10 studies (Kozel and George 2002) and a Cochrane review of 14 studies (Martin et al. 2003). The single negative study included only 6 reports with 91 subjects and, as such, had less power than most of the other meta-analyses (Couturier 2005). Despite finding differences between active and sham stimulation conditions, these studies have reported varying effect sizes and typically of modest clinical meaningfulness.

McNamara et al. (McNamara et al. 2001), conducted one of the first meta-analyses to evaluate the effectiveness of rTMS in mood disorders. A total of 16 published trials were considered, though 8 were excluded due to the absence of a randomized controlled group and 1 was excluded due to an ECT active comparator. Of the remaining 7 controlled trials of rTMS for depression, 5 involved rTMS delivered at 10 Hz or 20 Hz to the left frontal region, one study applied 1 Hz rTMS to the right hemisphere and in another both high and low frequency rTMS were applied. Collectively, it was demonstrated that the rTMS was beneficial compared to
placebo, with a number needed to treat of 2.3 with a 95% confidence interval 1.6 to 4.0; in a total 81 patients (McNamara et al. 2001).

Holtzhemier et al. (Holtzheimer et al. 2001) included 12 studies comparing the decrease in HDRS scores achieved with rTMS and sham stimulation. In twelve studies, the weighted mean effect size was 0.81 (95% CI: 0.42-1.20, p < .001). For studies using left DLPFC stimulation (11 studies), the weighted mean effect size was 0.89 (95% CI: 0.44-1.35, p < .001). For studies using left DLPFC stimulation in a parallel-groups design (7 studies), the weighted mean effect size was 0.88 (95% CI: 0.22-1.54, p < .01). No study showed a mean decrease in HDRS scores of greater than 50%, and the number of responders to rTMS (more than a 50% decrease in HDRS scores) across studies was small (13.7% with rTMS versus 7.9% with sham stimulation). The authors concluded that rTMS proved to be statistically superior to sham stimulation in the treatment of depression showing a moderate to large effect size. However, the clinical meaningfulness of these results was brought into question due to the modest overall change in symptoms.

Burt et al. (Burt et al. 2002) conducted a meta-analysis for three categories of studies in MDD patients: 1) open and uncontrolled trials, 2) sham or otherwise controlled trials, and comparisons of rTMS and ECT. For each study, the percentage change in HDRS scores and in one instance the Montgomery-Asberg Depression Rating Scale (MADRS) scores are reported. A meta-analysis of the nine open and uncontrolled studies, that reported quantitative changes in depression scores, revealed a weighted mean effect size (Cohen's $d$) of 1, corresponding to a large statistical effect. Again, despite the impressive consistency and large effect, the degree of therapeutic change across these studies was relatively modest. That is, the average reduction in HDRS or MADRS scores was only 37% (SD = 29). In fact, relatively few patients in these
studies would have met standard criteria for response (i.e., 50% reduction in symptoms), let alone remission.

Kozel et al (Kozel and George 2002) performed a meta-analysis on randomized sham-controlled trials of left prefrontal rTMS to treat depression as well as two previous meta-analyses of rTMS. Only studies that delivered left prefrontal rTMS were included. Of a total of 14 studies, 12 were included in the analysis with a moderate cumulative effect size of 0.53. The authors, however, highlighted the fact that although the mean change in HDRS scores for active rTMS was significantly different from sham the overall clinical effect was small.

Couturier et al. (Couturier 2005) conducted a meta-analysis of rTMS treatment articles that met a priori inclusion and exclusion criteria. A total of 6 studies were included in the meta-analysis, and 13 were excluded. Reasons for excluding rTMS depression articles included the following: (1) not using the HDRS-21 to evaluate treatment efficacy; (2) stimulation over areas other than the left DLPFC; (3) lack of an intent to treat analysis; (4) a treatment duration that was not 5–10 days; (5) concurrent treatment with antidepressant medications; (6) elderly subjects; and (7) inclusion of subjects with psychotic depression. On the basis of the 6 studies chosen for analysis, Couturier concluded that rTMS is not significantly better than placebo for TRD. However, several key issues must be considered before these findings are interpreted as definitive evidence for a lack of efficacy of rTMS for TRD. First, there is growing evidence that 2 weeks (i.e., 10 rTMS treatments) is likely insufficient to obtain substantive clinical improvement. As such, the findings of this meta-analysis may simply imply that 10 treatments, or 2 weeks of rTMS, are subtherapeutic for TRD. Second, excluding studies that used different versions of the HDRS or for the concomitant use of medications, while reasonable, greatly reduced the number of studies included in this meta-analysis. As such, a total of 91 subjects in 6
studies were included, which may have limited the power of this meta-analysis to find a significant difference between active-treatment and sham-treatment groups.

In one of the more recent meta-analyses, Gross et al. (Gross et al. 2007) examined whether there has been a change in the clinical effects induced by rTMS in depression through a systematic review and meta-analysis of literature from Dec 2005 to 2006. Studies were included using any frequency of rTMS and various depression scales were used including the HDRS, BDI and MADRS. Only five studies met criteria due to references excluded due to reviews, other diseases included, case reports, and the exclusion of a sham treatment. The authors compared this recent meta-analysis with that of Martin et al. (Martin et al. 2003) which included thirteen studies (234 patients) and showed a significant effect in decreasing depression scores favouring active rTMS when compared with sham rTMS (difference of -0.35; 95% CI -0.66 to – 0.44) after two weeks of stimulation of the left DLPFC. In this meta-analysis, however, there was significant heterogeneity of stimulation parameters used. The site, frequency and treatment duration (e.g., number of sessions varied from ten to sixteen) varied considerably from study to study. Also, most of the included studies recruited TRD patients; however, two of the selected studies did not recruit a treatment refractory group. Finally, only three of the five studies used an intention to treat analysis. The pooled effect size of this recent meta-analysis was - 0.76 (95% confidence interval, CI, -1.01 to –0.51), which was considerably larger than that of the earlier meta-analysis of Martin (Martin et al. 2003) (-0.35, 95% CI -0.66, t0 -0.44). Gross et al. (Gross et al. 2007) speculated that the larger effect size was due to an improved quality of more recent studies, that reflected optimized parameters of stimulation, more rTMS sessions and studies with larger sample sizes.

Lam et al. (Lam et al. 2008) conducted a comprehensive meta-analyses and identified 34 studies of which 24 were included in the meta-analysis (1024 patients) and included rTMS
studies up to May of 2008. Included studies involved all randomized control trials that were sham controlled of variable treatment duration. The authors reported that active rTMS condition had a significant risk difference for clinical response of 17% (n = 22 studies, 996 total patients) and for clinical remission of 14% (n = 16 studies, 795 total patients). Active rTMS resulted in an effect size of 0.48, a sizeable effect when considering that the majority of trials included in this meta-analysis were of either 1 or 2-week duration (i.e., 5 or 10 treatments). Slotema et al. recently performed a meta-analysis on 34 rTMS depression treatment studies (Slotema et al. 2010). They found a mean effect size of 0.55 (p < 0.01) and also suggested that monotherapy with rTMS was more effective than rTMS as an add-on. They also examined the relative efficacy of rTMS compared to ECT and concluded that rTMS was not as effective (mean effect size -0.47, p = 0.04). Interestingly, another recent meta-analysis of LFR rTMS found the pooled effect size to be similar to HFL (Schutter 2010). In this meta-analysis, nine studies including 252 subjects fulfilled inclusion criteria and were analyzed. A moderate, overall weighted mean effect size (d=0.63, 95% confidence interval=0.03-1.24) was found (Schutter 2010). Therefore, by combining LFR and HFL the therapeutic efficacy of rTMS may be enhanced.

4.2 Rationale for Further Investigation of Bilateral rTMS

Several lines of neurobiological evidence also support the use of bilateral rTMS. For example, the neurobiology of depression is not localized to the left DLPFC alone (Krishnan and Nestler 2008). Though there is much debate in the ECT literature regarding the efficacy of unilateral and bilateral treatment, it is clear that both forms of stimulation involve widely distributed neurobiological change as a consequence of seizure generalization (Nobler et al.
Imaging studies have demonstrated that MDD involves dysregulation of cortical activity with lower activity in the left DLPFC and higher activity in the right DLPFC (Baxter et al. 1989; Fitzgerald et al. 2008). Furthermore, neurophysiological studies using single and paired-pulse TMS have demonstrated asymmetrical differences in cortical excitability in depressed subjects compared to healthy controls (Bajbouj et al. 2006; Fitzgerald et al. 2004; Salustri et al. 2007). This has led to the assertion that both right and left (i.e. bilateral) dysregulation may underlie the neural circuitry of depression and need to be targeted by depression treatments in order to attain optimal therapeutic outcome (Rotenberg 2004; 2008).

5 Summary

TRD is a major public health problem in adults and later life. Despite advancements in pharmacotherapy a significant percentage of patients continue to suffer with intractable symptoms. The use of rTMS holds potential as a treatment for TRD. However, the evolution of the treatment parameters is ongoing and the optimal methods of stimulation are undetermined. The effect size of unilateral HFL or LFR rTMS to the DLPFC in meta-analyses varies depending on the patient population studied, length of treatment and parameters of stimulation. However, converging data from multiple studies suggest that treatment needs to occur for longer than two weeks with higher stimulation intensity. The largest multi-centre studies have shown statistically superior therapeutic effects over placebo however the response and remission rates have been modest. There is a strong rationale to compare sequential bilateral rTMS that combines both LFR and HFL to the conventional HFL treatment. The impressive response and remission rates in the Fitzgerald et al. (Fitzgerald et al. 2006a) study combined with the neurobiological
suggesting bilateral dysfunction in depression provide a compelling rationale to compare the efficacy of bilateral rTMS and unilateral HFL rTMS.
**Figure 1. DSM-IV Criteria for a Major Depressive Episode**

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

**Note:** Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

1. depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
2. markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
3. significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
4. insomnia or hypersomnia nearly every day
5. psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6. fatigue or loss of energy nearly every day
7. feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
9. recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
Figure 2. Thase and Rush Staging of Treatment-Resistant Depression

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Failure of at least one trial of an antidepressant from a major class of medication (i.e. SSRI)</td>
</tr>
<tr>
<td>Stage II</td>
<td>Stage I plus failure of an antidepressant from a separate class of medications than the medication used in Stage I</td>
</tr>
<tr>
<td>Stage III</td>
<td>Stage II resistance plus failure of a Tricyclic antidepressant</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Stage III resistance plus failure of a monoamine oxidase inhibitor</td>
</tr>
</tbody>
</table>
Chapter 3

Methods

The purpose of this chapter is to:

1. Provide an overview of the study design including sample selection and treatment protocol

2. Describe the primary and secondary outcome variables

3. Describe the approach to statistical analysis

6 Study Design

The study was a randomized, double blind, sham-controlled study. Subjects were randomized into three groups: sequential bilateral rTMS, unilateral rTMS and sham rTMS.

6.1 Subjects

Subjects were recruited from the Mood and Anxiety Disorders Program, Geriatric Mental Health Program and from posted flyers within the Centre for Addiction and Mental Health (a university teaching hospital that provides psychiatric care to a large urban catchment area and serves as a tertiary referral center for the province of Ontario). Subjects were recruited between January 1, 2006 and January 1, 2009. The inclusion and exclusion criteria are outlined in Table
1. Written informed consent was obtained from all patients on a form approved by the research ethics board of the Centre for Addiction and Mental Health.

6.2 Treatment Protocol

After enrolment and collection of baseline demographic and clinical data, individuals were randomized, using simple randomization, on a computer-generated list with the information stored on a central computer to one of three treatment arms (bilateral rTMS, unilateral rTMS and a sham control condition). By necessity, clinicians administering the treatment accessed the condition immediately prior to treatment initiation (and were aware of the treatment allocation). However, these clinicians were not involved in any other aspect of the study (i.e. recruitment or clinical evaluation). Subjects and raters were blind to randomization group. During the informed consent process subjects were told that there were three treatment conditions (two active and one placebo) and were instructed not to discuss their treatment with the clinical rater or other subjects. There was no mention in the consent as to the configuration of the placebo condition (i.e. unilateral or bilateral).

All subjects received 15 treatment sessions over the first 3 weeks of the study (5 days per week). Blinded clinical ratings occurred weekly. After the 15th treatment, the rater informed the treating clinician whether to continue treatment based on whether or not the subject achieved remission. If the subject met criteria for remission (score ≤10 on the 17-item HDRS), daily treatment ceased. Subjects who did not meet remission criteria continued in the acute phase of the study for 15 more treatments. If subjects missed 2 consecutive treatments (maximum interval between treatments of 4 days) they were discontinued from the treatment protocol.
Subjects were allowed to make up missed treatments; however, subjects were not allowed to miss more than 4 treatments for the duration of the study.

6.3 rTMS Treatment

rTMS was administered using a Medtronic Repetitive Magnetic Stimulator (Medtronic, Alpine Medical, California) and a hand-held 70-mm figure-of-8 coil. There was no change in machines for the duration of the study. Clinicians were instructed to have minimal interaction with the subjects. The resting motor threshold (RMT) for the abductor pollicis brevis muscle was measured prior to the first session with electromyographic recordings using the standard method of limits (Pascual-Leone et al. 1996; Rossini et al. 1994). The site of stimulation during the TMS sessions was defined by a point 5-cm anterior to that required for maximum stimulation of the abductor pollicis brevis along a parasagittal plane. Treatment stimulation was delivered at an intensity of 100% RMT in subjects younger than 60 years of age. Various studies have found that patients with late-life depression (LLD) have a higher degree of prefrontal atrophy than controls (Kumar et al. 2000; Schweitzer et al. 2001). Therefore, to overcome the anticipated effects of age-related prefrontal atrophy, the stimulation intensity, in subjects over age 60, was set at 120% RMT. This intensity was based on a previous study, which found that the average intensity required to overcome the effect of prefrontal atrophy was 114% RMT (Nahas et al. 2004). Treatment parameters adhered with safety guidelines (Chen et al. 1997b; Wassermann 1998) and are detailed in Table 2. The safety limit for train duration at 120% RMT is 3 seconds, thus, the pulses per train were altered in the over 60 age group. The total number of pulses at 100% and 120% were equivalent. The bilateral and unilateral conditions were roughly matched
for the amount of time of stimulation (at 100% RMT bilateral was LFR = 9 min and 10 sec, then HFL = 8 min and 13 sec and unilateral was HFL = 16 min and 22 sec, at 120% RMT bilateral was LFR = 9 min and 10 sec, then HFL = 13 min and 12 sec and unilateral was HFL = 25 min and 49 sec). Sham stimulation was applied with identical parameters to those for the unilateral (HFL) condition but with the coil angled at 90 degrees off the scalp in a single wing tilt position. This produced some scalp sensation and similar sound intensity to that of active stimulation. Subjects were unable to see the coil reducing the likelihood that they could detect the treatment condition. This method has been shown to produce a minimal degree of intracortical activity, but causes an auditory experience that is similar to active treatment (Lisanby et al. 2001). At the completion of the acute treatment phase, subjects were questioned about whether they thought they had received active or sham stimulation.

7 Assessments

Diagnosis and symptom severity were confirmed prior to study entry using the Structured Clinical Interview for DSM-IV (SCID). To confirm exclusion criteria, the antisocial and borderline personality disorders module of the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) was completed prior to study entry. To exclude a diagnosis of dementia (cut-off score of 26), the Mini Mental Status Exam was completed prior to study entry (Folstein et al. 1975).
7.1 Outcome Measures

The primary outcome for the study was remission of depression (dichotomous outcome). All subjects were assessed at baseline and after every 5 treatments up to 30 treatments with the 17-item HDRS. Remission was predefined as a final HRDS score \( \leq 10 \) at either 3 or 6 week follow-up. This score was chosen because this cut-off has been a standard in geriatric antidepressant trials (Kupfer 2005; Reynolds et al. 1996), ECT studies (Petrides et al. 2001), and depression treatment trials that have included patients across the lifespan (Meyers et al. 2009).

Secondary outcomes using the 17-item HDRS included rate of response (defined as a 50\% reduction in score), percent reduction in score and change in HDRS score over time. In addition, a battery of cognitive measures to assess short-term memory, attention and executive functioning were completed at baseline and at a study endpoint. The cognitive measures included the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al. 1998), Hopkins Verbal Learning Test revised (HVLT-R) (Brandt and Benedict 2001), Brief Visual Memory Test –Revised (BVMT-R) (Benedict 1997), and the Grooved Peg Board test (Matthews and Klove 1964).

8 Statistical Analysis

All statistical analyses were conducted using statistical software (SPSS for Windows 15.0; SPSS Inc. Chicago, Ill.) and the analysis was conducted on a modified intention-to-treat basis (Abraha and Montedori 2010). Continuous variables were analyzed with one-way analysis of variance (ANOVA). Categorical variables were analyzed with \( \chi^2 \) analyses or 2-tailed
Fisher’s exact tests (for dichotomous comparisons). All procedures were two-tailed and we used a significance level set at $\alpha = 0.05$ for the primary outcome.

Baseline differences in demographic and clinical variables were compared between treatment groups. Analysis of the primary outcome was performed using a $\chi^2$ test of association to determine whether remission rates differed across treatment conditions. Additional analyses of the primary outcome included 1) comparison of remission rates of each 2-way combination of treatment conditions and 2) adjustment for prognostically important baseline differences between treatment groups using a logistic regression model. A mixed model regression analysis was used to assess the change in HDRS score over time.
Table 1 Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th><strong>Inclusion Criteria</strong></th>
<th><strong>Exclusion Criteria</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Between the age of 18 and 85</td>
<td>(1) Had a history of DSM-IV substance dependence in the last 6 months (excluding nicotine), or DSM-IV substance abuse in the last month.</td>
</tr>
<tr>
<td>(2) Had a DSM-IV diagnosis of MDD without psychotic features based on the Structured Clinical Interview for DSM-IV (SCID)</td>
<td>(2) Met DSM-IV criteria for borderline personality disorder or antisocial personality disorder based on the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II)</td>
</tr>
<tr>
<td>(3) Had a score of greater than 21 on a 17-item HDRS.</td>
<td>(3) Met DSM-IV criteria for Bipolar I, II or NOS</td>
</tr>
<tr>
<td>(4) In the current depressive episode had failed to achieve a clinical response, or did not tolerate, at least 2 separate trials of antidepressants from different classes at sufficient dose for at least 6 weeks according to Stage II criteria outline by Thase et al. (Thase and Rush 1995)</td>
<td>(4) Had a significant unstable medical or neurologic illness or a history of seizures</td>
</tr>
<tr>
<td>(5) Receiving stable doses of psychotropic medications for at least four weeks prior to randomization.</td>
<td>(5) Acutely suicidal</td>
</tr>
<tr>
<td>(6) Capable to consent as assessed based on their ability to provide a spontaneous narrative description of the key elements of the study using the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR).</td>
<td>(6) Pregnant</td>
</tr>
<tr>
<td>(7) Currently an outpatient</td>
<td>(7) Metal implants in the cranium.</td>
</tr>
</tbody>
</table>

(8) Had a known diagnosis of dementia or a current MMSE score less than 26. |

(9) Had received the following psychotropic medications during the previous four weeks: benzodiazepines (dose equivalent ≥ lorazepam 2 mg/day), monoamine oxidase inhibitors, or buproprion. |

(10) Received prior treatment with rTMS (for any indication).
<table>
<thead>
<tr>
<th></th>
<th>Unilateral (HFL)</th>
<th>Bilateral (LFR then HFL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>100% RMT</strong></td>
<td>Frequency: 10Hz</td>
<td>Frequency: 1 Hz</td>
</tr>
<tr>
<td></td>
<td>Pulses Per Train: 50</td>
<td>Pulses Per Train: 100</td>
</tr>
<tr>
<td></td>
<td>Trains: 29</td>
<td>Trains: 4 + 1 (65 pulses)</td>
</tr>
<tr>
<td></td>
<td>Inter-train Interval: 30 sec</td>
<td>Inter-train Interval: 30 sec</td>
</tr>
<tr>
<td></td>
<td>Total Pulses: 1450</td>
<td>Total Pulses: 465</td>
</tr>
<tr>
<td></td>
<td><strong>Then</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency: 10Hz</td>
<td>Frequency: 10Hz</td>
</tr>
<tr>
<td></td>
<td>Pulses Per Train: 50</td>
<td>Pulses Per Train: 50</td>
</tr>
<tr>
<td></td>
<td>Number of Trains: 15</td>
<td>Number of Trains: 15</td>
</tr>
<tr>
<td></td>
<td>Inter-train Interval: 30 sec</td>
<td>Inter-train Interval: 30 sec</td>
</tr>
<tr>
<td></td>
<td>Total Pulses: 750</td>
<td>Total Pulses: 750</td>
</tr>
<tr>
<td><strong>120% RMT</strong></td>
<td>Frequency: 10Hz</td>
<td>Frequency: 1 Hz</td>
</tr>
<tr>
<td></td>
<td>Pulses Per Train: 30</td>
<td>Pulses Per Train: 100</td>
</tr>
<tr>
<td></td>
<td>Trains: 48 + 1 (10 pulses)</td>
<td>Trains: 4 + 1 (65 pulses)</td>
</tr>
<tr>
<td></td>
<td>Inter-train Interval: 30 sec</td>
<td>Inter-train Interval: 30 sec</td>
</tr>
<tr>
<td></td>
<td>Total Pulses: 1450</td>
<td>Total Pulses: 465</td>
</tr>
<tr>
<td></td>
<td><strong>Then</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency: 10Hz</td>
<td>Frequency: 10Hz</td>
</tr>
<tr>
<td></td>
<td>Pulses Per Train: 30</td>
<td>Pulses Per Train: 30</td>
</tr>
<tr>
<td></td>
<td>Trains: 25</td>
<td>Trains: 25</td>
</tr>
<tr>
<td></td>
<td>Inter-train Interval: 30 sec</td>
<td>Inter-train Interval: 30 sec</td>
</tr>
<tr>
<td></td>
<td>Total Pulses: 750</td>
<td>Total Pulses: 750</td>
</tr>
</tbody>
</table>
Chapter 4

Results

The purpose of this chapter is to:

1. Present and compare baseline clinical and demographic characteristics of the sample.

2. Present the rates of remission on the primary outcome variable in the three groups.

3. Present the response rates and rates of change among the three groups.

4. Present adverse event data among the three groups.

5. Present tolerability data and cognitive data among the three groups.

9 Participant Flow Through the Study

Of 159 patients screened, 33 did not meet eligibility criteria and 52 declined participation. A total of 74 patients were randomized (see Figure 3). After randomization, it was discovered that six subjects (2 in each group) had failed a course of ECT during the current depressive episode. These subjects were excluded from the analyses as having a more severe form of TRD that is thought to be highly unlikely to respond to rTMS (Brakemeier et al. 2007; Fitzgerald 2007). Indeed, large recent studies have excluded patients who have failed a course of ECT (George et al. 2010; O'Reardon et al. 2007). The remaining 68 subjects were included in the modified intention to treat analysis.
10 Baseline Clinical and Demographic Characteristics

The subjects’ baseline clinical and demographic characteristics are summarized in Table 3. We have not included statistics in this table as the CONSORT statement recommends that baseline characteristics between groups be presented descriptively (Moher et al. 2010; Schulz et al. 2010). Tests of significance assess the probability that the observed baseline differences could have occurred by chance, however, we already know that due to randomization the differences are caused by chance. The CONSORT statement suggests that such tests can mislead readers. Furthermore, the relatively small sample sizes of the three groups makes it difficult to delineate true differences because of limited statistical power. There were no clinically important differences between groups except for age: bilateral (58.0 ± 12.5), unilateral (48.9 ± 13.4), and sham groups (45.8 ± 13.4) (F_{65,2} = 5.65; p = 0.005). Because a higher proportion of subjects in the bilateral group were older, subjects in the bilateral group were more likely to be treated at 120% RMT and subjects in the unilateral and sham groups were more likely to be treated at 100% RMT. Forty-one subjects were taking antidepressant medication (with or without other agents) during the trial. There were no differences in the proportion of subjects taking any of the medication types among the three groups; 9 subjects had received treatment with ECT in previous depressive episodes. At 6 weeks, data on the primary outcome was available for n = 49 subjects (72.1%). Subjects who were lost to follow-up did not differ from retained subjects on any of the baseline clinical, cognitive or demographic variables.
11 Primary Outcome Variable

11.1 Remission

The remission rate (HDRS $\leq 10$) differed significantly among the three groups: bilateral (9 out of 26 subjects, 34.6%); unilateral (1 out of 22 subjects, 4.5%); and sham (1 out of 20 subjects, 5.0%) ($\chi^2 = 10.56; \text{df} = 2; p = 0.005$). The remission rate in the bilateral group was significantly higher than in the sham group (Fisher’s exact $p = 0.028$) and unilateral group (Fisher’s exact $p = 0.002$). The remission rate did not differ between the unilateral and the sham group (Fisher’s exact; $p = 0.48$). The remission rates stratified by age (over age 60 or under) are presented in Table 4. There were no differences between groups when the sample was stratified by age. The effect of treatment condition persisted after adjustment for baseline differences in age across groups ($p = 0.037$) and baseline differences in stimulation intensity ($p = 0.045$) in separate logistic regression models. In terms of time to remission, 4/9 subjects in the bilateral condition attained this endpoint at week 3, while 5/9 subjects required an additional three weeks of treatment to achieve remission (Table 4). In the completer analysis, the significant difference in remission rate across groups persisted ($\chi^2 = 7.83; \text{df} = 2; p = 0.02$). The remission rate was significantly higher in the bilateral group (9 out of 22 subjects, 40.9%) than in the sham group (1 out of 15 subjects, 6.7%) (Fisher’s exact $p = 0.028$) and approached significance when compared to the unilateral group (1 out of 12 subjects; 8.3%) (Fisher’s exact $p = 0.061$) and but did not differ between the unilateral and the sham group (Fisher’s exact; $p = 1.00$).
12 Secondary Outcome Variables

12.1 Response Rate

The proportions of responders on the HDRS differed significantly among the three groups: bilateral (10 out of 26, 38.5%); unilateral (1 out of 22, 4.5%); and sham (2 out of 20, 10.0%) ($\chi^2 = 10.39; \text{df}=2; p = 0.006$). The proportion of responders was significantly higher in the bilateral group than in the unilateral group (Fischer’s exact; $p = 0.003$) and sham group (Fischer’s exact $p = 0.022$). The proportion of responders did not differ between the unilateral and the sham groups (Fischer’s exact; $p = 1.00$). In the completer analysis, the overall findings remained unchanged: the proportions of responders on the HDRS differed significantly among the three groups: bilateral (10 out of 22, 45.5%); unilateral (1 out of 12, 8.3%); and sham (2 out of 15, 13.3%) ($\chi^2 = 7.42; \text{df}=2; p = 0.024$). Dichotomous comparisons between the bilateral and unilateral, as well as between the bilateral and sham, groups approached statistical significance (Fischer’s exact: $p = 0.053$ and $p = 0.073$ respectively). The proportion of responders did not differ between the unilateral and sham groups (Fischer’s exact; $p = 1.00$).

12.2 Percent Change in HDRS

As there were no significant differences between groups on baseline HDRS scores, we compared the percent change from baseline to endpoint of HDRS scores between groups. The mean (SD) decrease in HDRS score was 44.0% (30.5) in the bilateral group, 23.0% (13.2) in the unilateral group and 24.9% (24.5) in the sham group. There was an overall effect of group ($F_{58,2} = 5.26; p = 0.008$), with significant differences between the bilateral and unilateral groups.
(Tukey post-hoc; p = 0.015) and between the bilateral and sham groups (Tukey post-hoc test; p = 0.032). Unilateral and sham groups did not differ (Tukey post-hoc test; p = 0.97). The overall effect of treatment condition remained significant after adjusting for the effect of age as a continuous variable ($F_{58,2} = 3.84; p = 0.027$) and stimulation intensity ($F_{58,2} = 3.52; p = 0.036$) in successive ANCOVA models. Neither age ($F_{59,1} = 0.31; p = 0.58$) nor stimulation intensity ($F_{59,1} = 2.18; p = 0.15$) had a significant effect on percent reduction in their respective models.

### 12.3 Change in HDRS Over Time

The mean HDRS score at each weekly time point is presented in Figure 4. Mean and SD for each week of the study are presented in Table 5. A linear mixed model with HDRS score as the outcome was fitted to the data for weeks 1-6. This model included group (sham/unilateral/bilateral), time, group by time interaction, patient age (over or under 60) and baseline HDRS score (centered on its mean) as predictors. These models were fit using a heterogeneous compound symmetric covariance structure. Both the F-test for the interaction ($p = 0.22$) and the group by time parameter estimates for the Sham and Unilateral groups indicate that the rate of change in mean HAM-D score in these groups was not significantly different than that seen in the bilateral group. The difference between the weekly change in the bilateral group (decrease of 0.65 points per week) and the weekly change in the sham group (decrease of 0.24 points per week) is estimated to be 0.41 points (95% CI: [-0.17, 1.00]; $p = 0.16$). Similarly, the difference between the weekly change in the bilateral group (decrease of 0.65 points per week) and the weekly change in the unilateral group (decrease of 0.21 points per week) is estimated to be 0.44 points (95% CI: [-0.14, 1.03]; $p = 0.14$). It should be noted that the scores of subjects
who were in remission at the 3 week endpoint were not included in the mean scores calculated for weeks 4, 5 and 6 as these subjects were no longer undergoing experimental treatment.

13 Safety and Tolerability Profile

13.1 Cognition Ratings

No statistically significant change between the three groups was observed on any cognitive measures (see Table 6). Remitters showed a greater improvement in cognitive scores than non-remitters; however, these differences were not statistically significant (Table 7).

13.2 Adverse Effects and Drop-outs

As indicated, 19/68 subjects (28%) did not complete an endpoint assessment for the primary outcome: 4/26 in the bilateral treatment condition, 10/22 in the unilateral treatment condition and 5/20 in the sham control (See Figure 3). Details of the dropouts stratified by age are presented in Table 8. Three subjects withdrew after experiencing serious adverse events judged unrelated to rTMS treatment: one subject in the bilateral group after a myocardial infarction, two subjects who experienced suicidality requiring hospitalization (one subject in each of the unilateral and sham groups). One subject in the unilateral group withdrew due to insomnia, which may have been related to treatment or to depression. One subject in both the bilateral and sham group withdrew prior to a predefined end-point due to missing four consecutive treatments. The reason for the loss to follow up of the remaining 13 subjects
included lack of perceived benefit and inability to attend treatment sessions (N=2 in the bilateral group, N=8 in the unilateral group and N=3 in the sham group). With respect to adverse effects, one subject reported persistent scalp discomfort (unilateral) and one reported recurrent headaches (unilateral), though these subjects did not withdraw from the study.

14 Maintenance of the Blind

Of a total of 61 subjects who were assessed for maintenance of the blind, 35 subjects (57.4%) correctly guessed whether they received active or sham treatment: 16 (66.7%) in the bilateral group, 7 (36.8%) in the unilateral group and 12 (66.7%) in the sham group. These proportions did not differ significantly among the three groups ($\chi^2 = 4.76; \text{df} = 2; p=0.093$). The blinding of raters was not assessed.
### Table 3 Demographic and Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bilateral (n= 26)</th>
<th>Unilateral (n = 22)</th>
<th>Sham (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean, SD)</td>
<td>58.0 (12.5)</td>
<td>48.9 (13.4)</td>
<td>45.8 (13.4)</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>12/14</td>
<td>10/12</td>
<td>6/14</td>
</tr>
<tr>
<td>Recurrent episodes (%)</td>
<td>20 (76.9)</td>
<td>15 (68.2)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Current Episode Severe (%)</td>
<td>6 (23.1)</td>
<td>7 (31.8)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Current Episode Moderate (%)</td>
<td>20 (76.9)</td>
<td>15 (68.2)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Atypical Features (%)</td>
<td>1 (3.8)</td>
<td>2 (9.1)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>Melancholic Features (%)</td>
<td>4 (15.4)</td>
<td>0 (0)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Co morbid Anxiety (%)</td>
<td>3 (12.5)</td>
<td>1 (5.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SSRI (%)</td>
<td>6 (23.1)</td>
<td>8 (36.4)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>SNRI (%)</td>
<td>10 (38.5)</td>
<td>3 (13.6)</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>Tricyclic Antidepressant (%)</td>
<td>3 (11.5)</td>
<td>5 (22.7)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Mirtazapine (%)</td>
<td>3 (11.5)</td>
<td>2 (9.1)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Trazodone (%)</td>
<td>2 (7.7)</td>
<td>2 (9.1)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td>Group C</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Lithium Augmentation (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Atypical Antipsychotic Augment</td>
<td>5 (19.2)</td>
<td>2 (9.1)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Med Combination (%)</td>
<td>8 (30.8)</td>
<td>6 (27.3)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Benzodiazepine Use (%)</td>
<td>6 (23.1)</td>
<td>9 (40.9)</td>
<td>7 (35.0)</td>
</tr>
<tr>
<td>History of ECT (%)</td>
<td>3 (11.5)</td>
<td>3 (13.6)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>No Antidepressant (%)</td>
<td>8 (30.8)</td>
<td>5 (22.7)</td>
<td>10 (50.0)</td>
</tr>
<tr>
<td>Onset age (n = 43)</td>
<td>23.7 (13.5)</td>
<td>19.8 (12.0)</td>
<td>20.7 (10.1)</td>
</tr>
<tr>
<td>Number of Episodes (n=37)</td>
<td>2.6 (2.3)</td>
<td>2.9 (2.3)</td>
<td>3.8 (3.7)</td>
</tr>
<tr>
<td>One or more Medical Illnesses</td>
<td>10 (41.7)</td>
<td>9 (47.4)</td>
<td>8 (44.4)</td>
</tr>
<tr>
<td>Baseline HDRS</td>
<td>25.1 (3.8)</td>
<td>26.0 (3.3)</td>
<td>25.2 (2.8)</td>
</tr>
<tr>
<td>RBANS Total Score (mean, SD)</td>
<td>206.5 (23.3)</td>
<td>216.9 (24.9)</td>
<td>219.4 (28.1)</td>
</tr>
<tr>
<td>BVMT Percent Retention (mean, SD)</td>
<td>86.6 (36.0)</td>
<td>91.6 (17.0)</td>
<td>90.0 (13.3)</td>
</tr>
<tr>
<td>HVLT Percent Retention (mean, SD)</td>
<td>76.0 (23.9)</td>
<td>73.7 (22.6)</td>
<td>79.2 (23)</td>
</tr>
<tr>
<td>Pegboard (mean, SD)</td>
<td>91.2 (31.8)</td>
<td>85.4 (20.8)</td>
<td>76.4 (25.6)</td>
</tr>
</tbody>
</table>
Table 4  Remitters By Age

<table>
<thead>
<tr>
<th></th>
<th>Bilateral</th>
<th>Unilateral</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt; 60</td>
<td>Age &gt; 60</td>
<td></td>
</tr>
<tr>
<td>Baseline (n)</td>
<td>14</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Week 3</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Remission (n)</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Group Total</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Week 6</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Remission (n)</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Group Total</td>
<td>5</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>3**</td>
<td>6*</td>
<td>1**</td>
</tr>
<tr>
<td>Remitters (n)</td>
<td>3</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Group Total</td>
<td>9</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

*Over age 60: $\chi^2 = 5.12; \text{ df} = 2; \text{ p} = 0.077$

**Under age 60: $\chi^2 = 2.69; \text{ df} = 2; \text{ p} = 0.26$
Table 5  Mean HDRS scores (SD) by week

<table>
<thead>
<tr>
<th>Week</th>
<th>Bilateral (n = 24)*</th>
<th>Unilateral (n = 19)*</th>
<th>Sham (n = 18)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>25.1 (3.8)</td>
<td>26.0 (3.3)</td>
<td>25.2 (2.8)</td>
</tr>
<tr>
<td>1</td>
<td>17.1 (6.9)</td>
<td>20.4 (4.8)</td>
<td>19.5 (6.1)</td>
</tr>
<tr>
<td>2</td>
<td>14.8 (7.2)</td>
<td>19.5 (7.4)</td>
<td>18.7 (6.3)</td>
</tr>
<tr>
<td>3</td>
<td>15.3 (6.7)</td>
<td>19.6 (5.6)</td>
<td>17.8 (4.5)</td>
</tr>
<tr>
<td>4</td>
<td>14.8 (6.6)</td>
<td>19.4 (6.2)</td>
<td>18.1 (5.0)</td>
</tr>
<tr>
<td>5</td>
<td>13.8 (6.8)</td>
<td>19.4 (5.6)</td>
<td>18.6 (5.3)</td>
</tr>
<tr>
<td>6</td>
<td>14.4 (8.3)</td>
<td>20.3 (5.1)</td>
<td>18.9 (6.4)</td>
</tr>
<tr>
<td>Total (n) Completers</td>
<td>22</td>
<td>12</td>
<td>15</td>
</tr>
</tbody>
</table>

*subjects who dropped out prior to week one could not be included as they did not have a post baseline assessment
Table 6 Cognitive Change Scores

<table>
<thead>
<tr>
<th></th>
<th>Bilateral Mean (SD)</th>
<th>Unilateral Mean (SD)</th>
<th>Sham Mean (SD)</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 24</td>
<td>N = 19</td>
<td>N= 18</td>
<td></td>
</tr>
<tr>
<td>RBANS</td>
<td>2.0 (11.0)</td>
<td>-0.44 (15.4)</td>
<td>2.3 (15.0)</td>
<td>$F_{29,2} = 0.11; p = 0.89$</td>
</tr>
<tr>
<td>HVLT-R</td>
<td>4.8 (31.2)</td>
<td>-9.0 (21.5)</td>
<td>6.0 (23.8)</td>
<td>$F_{36,2} = 1.07; p = 0.35$</td>
</tr>
<tr>
<td>BVMT-R</td>
<td>-4.5 (39.3)</td>
<td>-4.9 (20.0)</td>
<td>-18.3 (24.2)</td>
<td>$F_{37,2} = 0.89; p = 0.42$</td>
</tr>
<tr>
<td>Grooved Peg Board</td>
<td>3.2 (11.9)</td>
<td>-2.1 (14.0)</td>
<td>2.3 (15.0)</td>
<td>$F_{38,2} = 0.84; p = 0.44$</td>
</tr>
</tbody>
</table>
Table 7 Cognitive Change Scores and Remission Status

<table>
<thead>
<tr>
<th></th>
<th>Remitters Mean (SD)</th>
<th>Non-Remitters Mean (SD)</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 11*</td>
<td>N= 50*</td>
<td></td>
</tr>
<tr>
<td>RBANS</td>
<td>2.4 (11.8)</td>
<td>1.1 (14.0)</td>
<td>$F_{30,1} = 0.05; p = 0.82$</td>
</tr>
<tr>
<td>HVLT-R</td>
<td>8.3 (31.1)</td>
<td>-0.6 (25.5)</td>
<td>$F_{37,1} = 0.81; p = 0.37$</td>
</tr>
<tr>
<td>BVMT-R</td>
<td>-3.1 (51.0)</td>
<td>-11.1 (20.4)</td>
<td>$F_{38,1} = 0.52; p = 0.47$</td>
</tr>
<tr>
<td>Grooved Peg Board</td>
<td>2.7 (13.4)</td>
<td>-0.2 (10.6)</td>
<td>$F_{39,1} = 0.50; p = 0.48$</td>
</tr>
</tbody>
</table>

*subjects who dropped out prior to week one could not be included as they did not have a post baseline assessment
Table 8 Dropouts By Age

<table>
<thead>
<tr>
<th></th>
<th>Bilateral</th>
<th>Unilateral</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt; 60</td>
<td>Age &gt; 60</td>
<td>Age &lt; 60</td>
</tr>
<tr>
<td>Baseline (n)</td>
<td>15</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Prior to Week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Dropout (n)</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Group Total</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Prior to Week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Dropout (n)</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Group Total</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Prior to week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Dropout (n)</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Group Total</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total Dropouts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n)</td>
<td>3</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Group Total</td>
<td>4</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Total Completed (n)</td>
<td>13</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Group Total</td>
<td>22</td>
<td>12</td>
<td>15</td>
</tr>
</tbody>
</table>
Figure 3. CONSORT Flow Diagram

1. Enrollment
   - Assessed for eligibility (n = 159)
     - Excluded (n = 85)
       - Did not meet inclusion criteria (n = 33)
       - Declined participation (n = 52)
     - Randomized (n = 74)

2. Allocation
   - Bilateral rTMS (n = 28)
     - All received at least one treatment session
   - Unilateral rTMS (n = 24)
     - All received at least one treatment session
   - Sham Control (n = 22)
     - All received at least one treatment session

3. Follow up
   - Discontinued Prior to Week 1 Assessment (n = 2)
   - Discontinued Prior to Week 3 Assessment (n = 1)
   - Achieved Endpoint Week 3 (n = 1)
   - Discontinued Prior to Week 6 Assessment (n = 1)
   - Completed Week 6 (n = 18)
   - Discontinued Prior to Week 1 Assessment (n = 3)
   - Discontinued Prior to Week 3 Assessment (n = 4)
   - Achieved Endpoint Week 3 (n = 1)
   - Discontinued Prior to Week 6 Assessment (n = 1)
   - Completed Week 6 (n = 11)
   - Discontinued Prior to Week 1 Assessment (n = 2)
   - Discontinued Prior to Week 3 Assessment (n = 1)
   - Achieved Endpoint Week 3 (n = 0)
   - Discontinued Prior to Week 6 Assessment (n = 2)
   - Completed Week 6 (n = 15)

4. Analysis
   - Analyzed (n = 26)
     - Excluded from analysis (n = 2 had ECT in the current episode)
   - Analyzed (n = 22)
     - Excluded from analysis (n = 2 had ECT in the current episode)
   - Analyzed (n = 20)
     - Excluded from analysis (n = 2 had ECT in the current episode)
Figure 4. Mean HDRS Change Scores
Chapter 5

Discussion

The purpose of this chapter is to:

1. Review the main findings of the study.

2. Outline the strengths of the study.

3. Outline and address the potential limitations of the study.

4. Outline potential explanations for the study results.

5. Describe the implications of the study results

6. Describe future plans to extend the findings of this thesis

15 Main Findings

To our knowledge this is the first randomized sham-controlled trial comparing sequential bilateral and unilateral rTMS that also controlled for medication initiation. We found that bilateral rTMS demonstrated superior efficacy to both unilateral rTMS and sham rTMS with a significantly greater number of subjects achieving remission and response in the bilateral group than in the unilateral and sham groups. Additionally, subjects treated with bilateral rTMS experienced a greater relative decrease in HDRS score than those in the unilateral and sham groups while subjects treated with either unilateral rTMS or sham rTMS did not differ on any
outcome measures. Furthermore, bilateral treatment was not associated with any cognitive side effects and was generally very well tolerated.

16 Strengths of the Study

The major strengths of this study are six-fold: 1) inclusion of “hard to treat” subjects with stage 2 or higher treatment–resistance (Thase and Rush 1995), 2) use of sham-rTMS to control for a placebo effect, 3) the comparison of a novel parameter configuration (sequential LFR then HFL) with the most common configuration (HFL), 4) careful attention to stimulation intensity in particular in relation to the subjects’ age, 5) treatment duration up to six weeks, 6) use of remission rates as a primary outcome.

17 Limitations

The main limitations included failed randomization (the mean ages of the subjects groups were significantly different across the three groups) as well as inadequate sample size to assess predictors of remission within each group. With the small sample in this study, the simple randomization did not yield balanced groups. A stratified randomization based on age would have yielded more balanced groups. Since a higher proportion of subjects in the bilateral group were older, subjects in the bilateral group were more likely to be treated at 120% of the MT and subjects in the unilateral and sham groups were more likely to be treated at 100% of the MT. Therefore, although the effect of treatment condition persisted after statistical control for age and
stimulation intensity, it remains possible that the observed superiority of bilateral rTMS over unilateral rTMS was due to the difference in stimulation intensity. In fact, since this study was designed, the field has moved toward use of higher stimulation intensity for all subjects to optimize treatment outcomes (Daskalakis et al. 2008). The limitation is, however, mitigated by the fact that MDD subjects over 60 are known to exhibit some degree of cortical atrophy, necessitating the use of higher intensities to counter this effect (Kumar et al. 2000; Nahas et al. 2004; Schweitzer et al. 2001). The targeting of the DLPFC may not have been accurate and may underlie the low remission rate in the unilateral group. In addition, the 5-cm rule for approximating the DLPFC, used in this study, has been shown to be imprecise in more recent imaging studies (Herbsman et al. 2009; Peleman et al. 2010; Rusjan et al. 2010). The imprecise targeting of the DLPFC may have biased the treatment in favour of the bilateral condition as these subjects had two chances of having stimulation correctly localized to the DLPFC whereas subjects in HFL only had one chance. Though medication initiation was controlled in this study, the possibility remains that subjects who started an antidepressant immediately before study entry may have experienced a delayed response (i.e. greater than 4 weeks) to their antidepressant during the trial (Rush et al. 2003). However, the majority of subjects, who were taking an antidepressant, had been on stable doses of medication for longer than 8 weeks. Furthermore, the variability in the use of any antidepressant may have impacted the effect of the treatment; however, previous work has shown a lack of an augmentation effect when rTMS is combined with antidepressants (Herwig et al. 2007). Prior adequacy of treatment was not assessed in our protocol, thus it is possible that subjects with “pseudo-treatment resistance” (subjects who had tolerated adequate doses for long enough durations) (Sackeim 2001) were included in the study. Using a measure of treatment adequacy, such as the antidepressant treatment history form (ATHF) (Oquendo et al. 2003), as an inclusion criterion would mitigate this potential limitation.
Another limitation may be the heterogeneity of the depression subtypes in the three groups (melancholic and atypical), however, the differences between the groups were not statistically significant. In addition, the rates of clinically significant anxiety, as measured by the SCID, were unexpectedly low for a sample of subjects with TRD. As anxiety symptoms are known to contribute to TRD, future studies should incorporate a validated scale to measure anxiety.

Though this study used a sham-control condition, the configuration of the sham technique used is less optimal than current techniques that involve simulation of the auditory and tactile experience of real TMS (George et al. 2010). Furthermore, the sham condition was configured as HFL only and this may have influenced the efficacy of the bilateral condition, as it was more complex than the other two conditions. Similar to all rTMS studies that use a sham procedure without an active coil, our study was compromised by the MT procedure in this group. In order to obtain the MT subjects have to undergo true TMS; therefore, some subjects (those with high MT’s in particular) may have been unintentionally unblinded by this experience. In fact, two thirds of subjects in the sham group successfully guessed their treatment condition. Future studies comparing bilateral and unilateral rTMS should consider having both sham configurations and an active sham coil. A potential explanation for the higher accuracy of guessing condition in the bilateral compared to the unilateral group is the higher remission rate, presumably subjects that improved would guess an active condition. Conversely, subjects in the unilateral condition, on average guessed that they were receiving sham stimulation. This is most likely related to the lack of improvement seen in this group. Unfortunately, we did not assess for reasons for the guess of condition in our assessment of maintenance of blinding. The relatively high sham response rate in our study may be related to the HDRS severity eligibility criteria. Recent data suggests that when comparing treatments for MDD, studies that include subjects with more severe depressive symptoms have lower placebo response rates (e.g., a score of $\geq 25$.
on a 17-item HDRS has been reported to minimize placebo response in previous medication trials) (Fournier et al. 2010). Therefore, our study did include patients with moderately severe symptoms and this may be a source of the high placebo response rate. However, the overall mean HDRS score across the groups was greater than 25.

18 Impact of the Findings

Notwithstanding these limitations, some of the results should be highlighted. The rates of remission with bilateral sequential treatment are a clinically meaningful finding given the broad age range and degree of treatment resistance in the sample. For example, the remission rate of 40.9% in the bilateral group was superior to all of the treatments investigated in the third and fourth level of the STAR*D study and comparable to the rates of remission at level two (Fava et al. 2006; McGrath et al. 2006; Nierenberg et al. 2006; Rush et al. 2006b; Trivedi et al. 2006). The high rates of remission with bilateral treatment may be attributable to the longer treatment course of rTMS (i.e., up to 30 treatments) than most previously published rTMS studies, supporting the notion that longer periods of stimulation are associated with improved efficacy for some subjects (Fitzgerald et al. 2003). In the bilateral group 4/9 subjects achieved remission at week 3, while an additional 5 remitted at week 6. This is congruent with recent studies suggesting that increasing the length of treatment or number of pulses leads to higher remission rates (George et al. 2010; O'Reardon et al. 2007).
19 Explanation of the Findings

A somewhat unexpected finding in this study was that HFL (i.e. unilateral) stimulation did not demonstrate superior efficacy compared to sham stimulation. To date the majority of rTMS studies investigating the use of unilateral HFL stimulation of the DLPFC have demonstrated reasonable though modest effect sizes (Schutter 2009). However, there have been a number of equivocal studies of HFL-TMS in TRD (Berman et al. 2000; Loo et al. 1999) and studies repeatedly report that the overall clinical results observed using unilateral rTMS are relatively modest. For example, a review by Holtzheimer et al. found a mean overall improvement of only 23.8% on the HDRS compared to 7.3% in the sham groups in blinded studies (Holtzheimer et al. 2001). This mild treatment effect was further emphasized by a meta-analysis reporting a mean HFL-rTMS response rate of 29.3% (Loo and Mitchell 2005). In sum, although efficacy studies evaluating HFL-rTMS to date suggest that while this treatment is therapeutically effective, the magnitude of this clinical effect remains modest. That our study failed to demonstrate a difference between HFL and sham stimulation may be related to the conservative treatment parameters used in this group (1450 pulses per day and 100% RMT intensity for most subjects). From a neurobiological standpoint, higher intensity treatment (i.e. 120% RMT) induces much greater trans-synaptic activation than 100% RMT or 80% RMT (Nahas et al. 2001). The number of pulses in the current study is less than half the number used in two recent multi-centre studies (George et al. 2010; O'Reardon et al. 2007). We also hypothesize that the low remission rate in the unilateral group combined with the extensive 6-week duration of double blind conditions contributed to the unusually high dropout rate observed in the study. In fact, the majority of dropouts in the unilateral condition gave “lack of benefit” as
their reason for discontinuing treatment. Though not statistically different from the other two groups, the drop out rate in the unilateral group was 45%.

Neurobiological mechanisms may also underlie the superior efficacy of sequential bilateral rTMS. Although rTMS has widely distributed effects through intracortical connectivity, the DLPFC is the intended target in depression treatment trials due to its putative role in the pathophysiology of depression. However, varying amounts of both right-sided and left-sided DLPFC dysregulation are found in patients with depression (Baxter et al. 1989; Fitzgerald et al. 2008; Kimbrell et al. 1999; Speer et al. 2000). Chen et al. (Chen et al. 1997a) have demonstrated that low frequency rTMS stimulation for a period of approximately 15 minutes induces a transient inhibition of the cortex, thus providing a mechanism to address the right-sided hyperfunction found in depression. In contrast, high frequency stimulation has been shown to increase excitability, thus providing a therapeutic tool to address left-sided dysregulation (Fitzgerald et al. 2006b; Pascual-Leone et al. 1994). Kimbrell et al.(Kimbrell et al. 1999) examined the possibility that a subset of depressed patients with cerebral hypometabolism would respond to high frequency rTMS whereas patients with cerebral hypermetabolism would respond to low frequency rTMS, thus attempting to target treatment to potential underlying cerebral pathophysiology. Thirteen subjects participated in a randomized crossover trial of 2 weeks in which cerebral metabolism was assessed using [18F]-Fluorodeoxyglucose positron emission tomography (PET) scans. They found that patients with baseline hypometabolism responded better to high frequency rTMS stimulation compared to patients with baseline hypermetabolism, who had tended to have a better response to low frequency rTMS. These results provide a rationale for the use of a bilateral form of rTMS to address both hypofunction in left PFC and hyperfunction in the right PFC. It is possible, therefore, that the modest efficacy of LFR and HFL rTMS alone may be related to the underlying DLPFC dysregulation in each individual
patient (i.e. certain patients may have more prominent right-sided dysregulation and may not improve with HFL alone). The superior efficacy of sequential bilateral rTMS may simply reflect the fact that sequential bilateral rTMS targets both types of DLPFC dysregulation.

Another important finding of the present study is, in contrast to previous literature suggesting that age is a negative predictor of treatment efficacy using rTMS (Fregni et al. 2006), the positive response to treatment in subjects over the age of 60. Although relatively few published rTMS studies have included subjects over the age of 60, existing studies have likely been limited by suboptimal stimulation parameters (i.e. intensity 80 – 100% RMT) and insufficient treatment durations (Manes et al. 2001; Mosimann et al. 2004). A separate study found that response to rTMS was related to the degree of prefrontal atrophy and recommended that stimulation intensity be adjusted to overcome this age-related effect (Mosimann et al. 2002). Following this, Nahas et al. (2004) used an open design in which they adjusted stimulus intensity based on coil-to-cortex distance (114% average required) in 18 older subjects and found a 26% remission rate (Nahas et al. 2004). Similarly, a recent large randomized controlled trial found unilateral rTMS at 110% stimulation intensity resulted in a similar remission rate in an elderly sample with cerebrovascular pathology (Jorge et al. 2008). To our knowledge, there are no published studies of bilateral rTMS in subjects over the age of 60. This study suggests that bilateral rTMS at 120% of RMT in subjects in this age group is not only well tolerated but clinically efficacious as 50% of the subjects, over age 60, who received bilateral treatment, achieved remission.
Conclusion and Future Directions

In summary, although there were some major limitations to the present study, the results demonstrate that sequential bilateral rTMS is safe and effective for individuals with treatment-resistant depression across the lifespan. The remission rate found in the bilateral group was higher than remission rates found in the large multi-centre studies (George et al. 2010; O'Reardon et al. 2007) and consistent with the higher remission rate in the Fitzgerald study (Fitzgerald et al. 2006a). Due to methodological flaws, we were not able to fully distinguish the effect of bilateral treatment from the effect of higher stimulation intensity. However, the efficacy of sequential bilateral stimulation (after statistical adjustment for increased stimulation intensity) in this study and the study by Fitzgerald (Fitzgerald et al. 2006a) suggests that future studies should examine the relative efficacy of unilateral rTMS and bilateral rTMS to determine if bilateral treatment is a mechanism to increase the relatively modest remission rates that have been found with unilateral rTMS. In addition, our study lends support to the hypothesis that higher stimulation intensity may be necessary for rTMS treatment in older patients. The response and remission rate in the over 60 group suggests that bilateral rTMS may be an important parameter configuration to pursue in future controlled studies in this population. The pathophysiological disturbance in late-life depression may be more widely distributed than in younger adults and therefore, may be more likely to respond with this form of treatment.

Examination of the underlying neurobiological mechanisms of unilateral and bilateral rTMS may provide further insight in this regard. The addition of a functional neuroimaging component to future clinical treatment trials may help to clarify the differential therapeutic effects of these two forms of stimulation. In addition to functional imaging changes, certain patterns of cortical inhibitory dysregulation have been shown to predict treatment.
resistance (Levinson et al. 2010). Future rTMS studies may consider incorporating these relatively quick neurophysiological tests to see if they predict treatment response and to determine if cortical inhibitory dysregulation changes with rTMS as it does with ECT and some medication treatment (Sanacora et al. 2003; Sanacora et al. 2002).

Another potential direction for future studies is to compare the relative merits of targeting the DLPFC with MRI co-registration (Fitzgerald et al. 2009) and using improved methods of approximation (Herbsman et al. 2009; Rusjan et al. 2010). In this study we used increased intensity to attempt to overcome prefrontal atrophy, however, not all adults over age 60 have prefrontal atrophy. MRI imaging allows for more accurate localization of the DLPFC with co-registration and provides the potential to correct for the coil-to-cortex distance (Stokes et al. 2007). However, the excess cost and time of using MRI co-registration and coil-to-cortex correction to optimize therapeutic outcomes may make rTMS prohibitive to the broader population of patients with TRD.

Interestingly, a novel coil configuration has been developed that generates a magnetic field that penetrates deeper into the brain. The H-Coil is designed to stimulate deeper neuronal pathways in the affective circuit such as fibers connecting the anterior cingulate, orbitofrontal and prefrontal cortex with the nucleus accumbens and ventral tegmental area. Extensive engineering and mathematical modeling were completed in order to optimize the coil design for maximizing the percentage of stimulation in depth relative to the cortical regions (Roth et al. 2002). Standard figure-8 coils that have been used in previous depression rTMS studies primarily demonstrate a physiological effect in superficial cortical regions. However, the intensity of the electric field decreases rapidly with greater distance from the coil (Eaton 1992; Maccabee et al. 1990; Tofts 1990; Tofts and Branston 1991) (Figure 5). Therefore, in order to
stimulate the deeper cortical and subcortical structures involved in depression, higher intensities are needed in figure-8 coils. Such high intensities, however, are often associated with excessive cortical stimulation leading to undesirable side effects (i.e., scalp discomfort, headache, syncope, seizures) and excessive coil heating.

Zangen et al. (2005), performed the first study of the H-Coil at the National Institute of Health (Zangen et al. 2005). The physiological profile and safety of the H-Coil was examined in healthy volunteers. The H-Coil was compared to a regular figure-8 coil in 6 healthy volunteers by measuring thresholds for activation of the APB representation in the motor cortex as a function of distance from each of the coils. The findings of this study indicated that the rate of decrease of magnetic intensity is markedly slower for the H-Coil compared to a figure-8 coil (see Figure 5). This study confirmed the theoretical calculations and phantom brain measurements indicating the ability of the H-Coil to stimulate brain structures at much greater distance than the standard figure-8 coil (Zangen et al. 2005). None of the 6 subjects who participated in the study reported any significant side effects after the TMS session. No changes in cognitive functioning or hearing were found (Zangen et al. 2005). One of the 6 subjects reported a slight, transient headache.

A second safety study further compared the H-coil with a standard figure-8 coil (Quadstim; manufactured by MagStim) and a sham coil by stimulating the cortex with 1Hz, 10 Hz and 20 Hz in healthy adults (Levkovitz et al. 2007). Thirty-one subjects completed the entire experimental course with three dropouts occurring after the first visit (1 Hz stimulation) for reasons unrelated to the study. All forms of TMS stimulation were well tolerated with no major side effects. There were no reports of emergent seizure induction, local pain of the scalp, transient headache, dizziness, transient hypotension, visual disturbances, weakness, parenthesis,
instability, vertigo, tinnitus, or other bodily sensations. In addition, the clinical inspection of the scalp area, conducted immediately after each stimulation session, showed no evidence of skin irritation. Auditory thresholds measured by audiograms (conducted pre and post TMS treatments) indicated no auditory threshold shifts, indicating no hearing loss in any of the subjects. Similarly, there were no significant changes in additional physical measures, such as hemodynamic measures (blood pressure and heart rate), perceived headache intensity and general neurological measures (e.g., time to walk 5m forward, backward, etc.). This safety study analyzed relative transient cognitive effects (i.e., tests of spatial-motor performance, attention, memory and executive functions). Improvements in cognitive performance were found with each treatment visit likely related to learning rather than the effects of the H-coil. Cognitive performance did not differ among subjects who received H-Coil, figure-8 coil and sham stimulation. Subjects did not experience cognitive deterioration. Additionally, the emotional effects of stimulation were evaluated using a 20-item self-report measure monitoring changes in affective state (Watson et al. 1988). The study demonstrated an increase in subjects' positive emotions, with the H-Coil. There was no evidence for persistent changes in negative affect or feelings of dissociation.

The first study of safety and feasibility of H-Coil rTMS in TRD was recently published (Levkovitz et al. 2009). Three different H-Coil designs were tested (H1 coil, H2, and H1L-coil). The H1-coil stimulates the prefrontal cortex (PFC) bilaterally, but gives distinct preferential stimulation to the deep layers of the left PFC, while also stimulating the right prefrontal cortex. The H2-coil stimulates both left and right PFC equally. The H1L-coil provides only left unilateral stimulation of the dorsolateral and ventrolateral PFC. The H1L-coil was further examined under two different levels of intensity: 110% and 120% of RMT. Sixty-five patients were enrolled and randomly assigned to four separate groups: H1 stimulation (24 subjects), H2
stimulation (22 subjects), H1L-110% stimulation (8 subjects), and H1L-120% stimulation (11 subjects). Fifty-eight subjects completed the protocol and were analyzed. Subjects underwent a drug medication taper-down period of 10 to 14 days, followed by daily treatment (parameters: 20Hz, 2s on 20s off, for 20 minutes, i.e., 1680 pulses) each weekday for 4 consecutive weeks. There were weekly follow-up visits during treatment and at one-week after the end of 4 weeks of treatment. Efficacy, tolerability and safety measures were conducted as part of the active treatment phase and follow-up visits. Overall, H1-coil and H1L-120%-coil treatment groups experience the most improvement. The response rate on the HDRS-21 were as follows: 47% in the H1-Coil group, 30% in the H2-coil group, 0% in the H1L-110%-coil group and 60% in the H1L-120%-coil group. The remission rates (defined as an HDRS-24 score of 10 or lower) for the H1, H2, H1L-110% and H1L-120% Coil groups were 42%, 10%, 0% and 50%, respectively. A statistically significant difference between the treatment groups was found in the change from HDRS baseline score over time ($F_{58,3} = 6.42; p = 0.0008$). The mean reduction per treatment group was estimated from the model as -12.3 points in the H1 coil group, -6.78 in the H2 coil group, no change in the H1L-110% group and -7.6 in the H1L-120% group. Overall, clinical improvement across groups was most pronounced in the older subjects age 50 to 65 years. Improvement was evident in the majority of subjects between the first and second week of treatment. Patients did not report any pain or discomfort in any of the H-Coil groups. There were no changes in blood pressure, seizures or neurological problems. Two patients reported mild transient headaches. These results suggest that stimulation with the H1-Coil at 120% intensity is most likely to provide maximal therapeutic benefit in the treatment of depression. The properties of the magnetic field generated by the H1-Coil and its ability to stimulate bilaterally, holds potential for the future of rTMS in patients with TRD, but may also provide a more optimal form
of TMS in LLD due to its ability to overcome prefrontal atrophy and target deeper structures in the prefrontal cortex.
Figure 5. Intensity of Magnetic Field as a Function of Distance from the Coil
References


Fitzgerald PB. 2007. Repetitive transcranial magnetic stimulation is not as effective as electroconvulsive therapy for major depression. Evid Based Ment Health 10:78.


Matthews CG, Klove H. 1964. Instruction manual for the Adult Neuropsychology Test Battery. (University of Wisconsin Medical School., Madison, WI).


Slotema CW, Blom JD, Hoek HW, Sommer IE. 2010. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry 71:873-84.


