The relationship between seizure adequacy and response to magnetic seizure therapy in patients with treatment-resistant depression

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science

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Magnetic Seizure Therapy (MST), an alternative to electroconvulsive therapy (ECT), is under investigation for the treatment of depression, and the optimal treatment frequency is still unknown. Electrophysiological (EEG) recordings during treatment seizures can predict response to ECT, but the relationship between seizure characteristics and treatment outcome in MST remains unclear. This study aims to investigate the effect of stimulation frequency on seizure characteristics in MST, and to elucidate the relationship between seizure characteristics and MST treatment outcome. The results indicate that 100 Hz seizures had the lowest quality characteristics than the 25 and 50 Hz groups, particularly with measures of seizure duration. Moreover, shorter polyspike durations and slow-wave amplitudes are correlated with better treatment outcome, but these measures do not significantly differ across frequency groups. The results suggest MST may not have the same mechanisms of action compared to ECT, and that frequency is not an important modifier of treatment response.
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Contributions

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Julia Dimitrova, Ankita Dubey, Cinthia Romeros, Stacey Shim, and Mawahib Semeralul were responsible for clinical and cognitive data collection. Dr.s Daphne Voineskos, Albert Wong, David Goldbloom, Daniel Blumberger, Jeff Daskalakis administered the treatments. Dr.s Yuliya Knyanyska and Moshe Isserles assisted with patient consultations. Clinical team members, Joanna Burns, Sheila Bartlett, David Tennant and Daniel Phung managed treatment sessions and patient safety.

Felicity Backhouse learned to visually read EEG recordings under the supervision of Dr. Yoshihiro Noda, and Felicity Backhouse created the additional rating scales to be used in conjunction with previous rating scales for ease of use. Felicity Backhouse scored all paper EEG traces, and Dr. Noda helped to clarify ratings for ambiguities arising from approximately 1-2% of traces. Felicity Backhouse and Daniel Blumberger were responsible for overseeing the digitized ictal EEG data collection. Statistical Consultations with Dr. Marcos Sanchez assisted with the selection of appropriate statistical tests. Felicity Backhouse performed all data analysis, interpretation and drafting of the thesis document under the guidance of Dr. Blumberger. Program Advisory Committee (PAC) members Dr. Daskalakis and Dr. Faranak Farzan gave feedback on the written thesis document.

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<tbody>
<tr>
<td>µV</td>
<td>Microvolt</td>
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<tr>
<td>5-HT</td>
<td>Serotonin</td>
</tr>
<tr>
<td>ACC</td>
<td>Anterior Cingulate Cortex</td>
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<td>AMI</td>
<td>Autobiographical Memory Interview</td>
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<tr>
<td>BDNF</td>
<td>Brain Derived Neurotrophic Factor</td>
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<tr>
<td>BOLD</td>
<td>Blood Oxygenation Level Dependent signal</td>
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<tr>
<td>BPD</td>
<td>Bipolar Depression</td>
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<tr>
<td>Ca++</td>
<td>Calcium Ion</td>
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<tr>
<td>CAMH</td>
<td>Centre for Addiction and Mental Health</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
</tr>
<tr>
<td>DA</td>
<td>Dopamine</td>
</tr>
<tr>
<td>DLPFC</td>
<td>Dorsolateral Prefrontal Cortex</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 4th Edition</td>
</tr>
<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 5th Edition</td>
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<tr>
<td>ECT</td>
<td>Electroconvulsive Therapy</td>
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<tr>
<td>ECS</td>
<td>Electroconvulsive Shock</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<tr>
<td>EMG</td>
<td>Electromyography</td>
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<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
</tr>
<tr>
<td>Glu</td>
<td>Glutamate</td>
</tr>
<tr>
<td>GPe</td>
<td>External Globus Pallidus</td>
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<tr>
<td>GPI</td>
<td>Globus Pallidus Internus</td>
</tr>
<tr>
<td>HAMD</td>
<td>Hamilton Depression Rating Scale</td>
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<tr>
<td>H-MRS</td>
<td>Proton Magnetic Resonance Spectroscopy</td>
</tr>
<tr>
<td>HPA</td>
<td>Hypothalamic-Pituitary-Adrenal</td>
</tr>
<tr>
<td>HVA</td>
<td>Homovanillic Acid</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IPSPs</td>
<td>Inhibitory Post-Synaptic Potentials</td>
</tr>
<tr>
<td>K+</td>
<td>Potassium ion</td>
</tr>
<tr>
<td>LC</td>
<td>Locus Coeruleus</td>
</tr>
<tr>
<td>M</td>
<td>Mean</td>
</tr>
<tr>
<td>MAOIs</td>
<td>Monoamine Oxidase Inhibitors</td>
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<tr>
<td>MDT</td>
<td>Medial Dorsal Thalamus</td>
</tr>
<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
</tr>
<tr>
<td>mg</td>
<td>milligrams</td>
</tr>
<tr>
<td>MMECT</td>
<td>Multiple Monitored ECT</td>
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<tr>
<td>MoCA</td>
<td>Montreal Cognitive Assessment</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>MST</td>
<td>Magnetic Seizure Therapy</td>
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<tr>
<td>mV</td>
<td>millivolt</td>
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<tr>
<td>ms</td>
<td>milliseconds</td>
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Na+ Sodium ion
NAcc Nucleus Accumbens
NE Norepinephrine
NMDA N-methyl-D-aspartate
OCD Obsessive Compulsive Disorder
OFC Orbitofrontal Cortex
OFG Orbitofrontal Grey
PET Positron Emission Tomography
PFC Prefrontal Cortex
QIDS Quick Inventory of Depressive Symptoms
Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire
RBANS Repeated Battery for Neuropsychological Status
REB Research Ethics Board
rTMS Repetitive Transcranial Magnetic Stimulation
RUL ECT Right Unilateral Electroconvulsive Therapy
s Seconds
SD Standard Deviation
SE Standard Error
SCID-IV Structured Clinical Interview for DSM-IV
SPECT Single-Photon Emission Computerized Tomography
SPSS Statistical Package for Social Sciences
SNRIs Serotonin-Norepinephrine Reuptake Inhibitors
SSI Scale for Suicidal Ideation
SSRIs Selective Serotonin Reuptake Inhibitors
STN Subthalamic Nucleus
STDP Spike-Timing Dependent Plasticity
TCAs Tricyclic Antidepressants
TMS Transcranial Magnetic Stimulation
TRD Treatment Resistant Depression
TNF Tumor Necrosis Factor
VMPFC Ventro-medial Prefrontal Cortex
VTA Ventral Tegmental Area
V/cm Volts per centimeter
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Chapter 1: Literature Review

1.1 Major Depressive Disorder

Major Depressive Disorder (MDD) is a global public health problem (Whiteford et al., 2013), and has cost the Canadian economy more than $14.4 billion dollars (Lim and Dewa, 2008). A diagnosis of MDD puts individuals at a heightened risk of suicide- a risk approximately 25 times greater than the general population (Friedman and Leon, 2007), with as many as 15% of those with an MDD diagnosis commit suicide (Simon and Vonkorff, 1999).

According to the DSM-5, one of the following two symptoms must be present for at least two weeks to confirm a diagnosis of depression: 1) a loss of interest in things once found pleasurable, otherwise known as ‘anhedonia’, or 2) the presence of depressed mood. Additionally, the existence of 4 or more cognitive, emotional, and somatic symptoms are required to confirm a diagnosis of depression, including: 1) sleep quality and quantity, 2) psychomotor retardation or agitation, 3) weight fluctuations, 4) lethargy, 5) feelings of worthless, hopeless, or guilt, 6) an inability to concentrate, and 7) thoughts of death or suicide (APA, 2013).

Due to the broad range of symptoms involved in diagnosis, MDD is a heterogeneous mental health disorder and different individuals require different methods of treatment. It is therefore important to understand theories of depression to formulate adequate treatment strategies targeting different systems. Moreover, while many patients respond to primary interventions, tertiary efforts are needed for those with treatment resistant depression (TRD), defined as those who fail to respond to at least two classes of antidepressants of sufficient dose and length (Al-Harbi, 2012), and make up to one third of patients with MDD diagnoses. The wide number of
pharmaceutical targets that have been investigated suggest that there are multiple complex biological processed that can lead to depression.

**Early Pharmaceutical Treatments for Depression**

The first pharmaceuticals investigated for use in depression was the class of drugs known as monoamine oxidase inhibitors (MAOIs). MAOIs inhibit the enzyme responsible for catabolizing the monoamine neurotransmitters, and extends the time that amine molecules are intact and able to bind with receptors at the synapse (Ramsay and Tipton, 2017). MAOIs affect amines involved in mood, including dopamine, norepinephrine and serotonin However, as MAOIs also work to inhibit other amines, such as tyramine, phenylethylamine, histamine, and epinephrine, serious side effects have been noted, and the use of this medication requires many dietary restrictions (Brown et al, 1989) and caution with pharmaceutical interactions (Krings-Ernst et al, 2013). In fact, due to the vast array of dangerous interactions, patients taking MAOIs are at a heightened the risk of overdose and mortality (Gahr et al, 2013). For this reason, MAOIs are rarely prescribed today, and are only used as a last resort for those who do not respond to other forms of antidepressants.

The second class of antidepressants to be developed were tricyclic antidepressants (TCAs), and were named after their chemical structure. TCAs block the uptake of serotonin (5-HT), and to a lesser degree, norepinephrine (NE), leaving more of these neurotransmitters available for synaptic binding (López-Muñoz and Alamo, 2009). The use of TCAs mitigated the need for MAOI use, as similar response rates were noted with a lowered risk of severe side effects (Blackwell, 1981).

These served as the first-line treatment for depression for many years, until the breakthrough development of fluoxetine (Montgomery, 1985). Fluoxetine was the first selective serotonin reuptake inhibitor (SSRI) to ever be developed, and was unique for its ability to inhibit the uptake of 5-HT without directly interfering with other
neurotransmitter systems. This level of specificity allowed for a reduced side effect profile compared to MAOIs and TCAs (López-Muñoz et al, 2009), and as such, largely replaced the use of both medications in first-line interventions. Despite further developments, fluoxetine has remained a first-choice treatment option for patients with MDD. The ability of these early pharmaceuticals to cure depression helped to formulate one of the most popular theories of depressions pathophysiology.

### 1.2 Biological Theories of MDD Pathophysiology

During the Freudian revolution, the suggestion that depression is the result of biological problems was largely rejected by the medical community in favor of psychoanalytic theories (Friedman, 1977). For many years, pharmaceutical industry efforts were focused on treatments for schizophrenia (SCZ) (Guertin et al, 1960), but a serendipitous discovery lead to the development of the first pharmaceutical antidepressant (Schiele, 1963). It has been over 60 years since the first use of MAOI, and the medical industry has continued to develop new targets for treatment and advance our understanding of depression. Below, some of the most prominent biological theories of depression and their associated pathophysiology. It is important to note this list is not exhaustive or complete. The medical field is making great efforts to increase specificity in the selection of first line treatments, and combining information gained from each of these biological investigations can lead to individualized treatment options for those with distinct subtypes of pathophysiology.

#### Monoamine Hypothesis of Depression

The monoamine hypothesis is among the oldest and most well-studied biological theories of the depression. This theory suggests the disorder arises from
abnormalities in the function of the monoamines, namely 5-HT, dopamine (DA) and NE. Decades of research on these neurotransmitter systems have revealed information about their biological mechanisms; 5-HT is thought to be responsible for sleep, impulse, irritability, and learning and memory (Hendren and Butler, 2013); DA, has demonstrated involvement in movement, motivation, and reward (Nestler and Carlezon, 2006), and NE is released during fight and flight responses (Checkley, 1988) (Brunello et al, 2003). There is ample evidence to suggest these monoamines are involved in the onset of depression due to their biological involvement in most depressive symptoms, including anhedonia, anxiety, low motivation, difficulty sleeping, and irritability. Evidence for their individual involvement is detailed in the following sections.

**Serotonin**

Genetic Predispositions

5-HT involvement in depression is well established. Serotonin reuptake inhibitors (SSRIs) are often the first-line of treatment for depression due to their reduced side effects, and genetic predispositions to 5-HT dysregulation have been identified as a risk factor for depression, suggesting serotonin dysfunction may be a route cause of depression in patients with these genetic predispositions, and increasing the 5-HT bioavailability can help mitigate that problem. For instance, individuals with certain polymorphisms in the gene coding for the serotonin transporter have a heightened risk of developing depression throughout their lifetime (Ogilvie et al, 1996). These polymorphisms have been shown to affect the efficiency of gene transcription (Iurescia et al, 2016) and result in decreased 5-HT receptors in binding locations (David et al, 2005). They have also been specifically associated with anxiety-related traits in depression (Lesch et al, 1996). While not all individuals with these
polymorphisms go on to develop depression, they are particularly susceptible to developing the disorder after stressful life events (Risch et al, 2009), demonstrating the interaction of several factors in the development of the disorder.

Endogenous 5-HT Levels in Depression
Evidence suggests an association between serotonergic levels in the blood stream and MDD. Victims of suicide displayed 44% more 5HT₂ receptors in the frontal cortex relative patients who died of other causes (Stanley and Mann, 1983), and research has shown patients with depression have blood platelet serotonin receptors that are deemed ‘supersensitive’ to binding (Brusov et al, 1989).

Dopamine

Dopamine is involved in many neurological systems, and deficiency may be coupled with symptoms such as general low mood, amotivation (Salamone et al, 2016), cognitive and concentration difficulties (Volkow et al, 2009), fatigue (Dobryakova et al, 2015), general apathy (Thobois et al, 2013) and anhedonia (Salamone et al, 1997). These behavioural symptoms make up the majority of the features characterizing major depressive disorder (APA, 2013). Although these symptoms may also arise from depletions in other catecholamines (Hirschfeld, 2000), a pertinent role of dopamine dysregulation has been identified as a direct cause of many individuals with depression, demonstrated by the fact that MDD individuals with baseline dopaminergic abnormalities will benefit significantly more from a dopamine agonists and dopamine reuptake inhibitors such as wellbutrin and bupropion, relative to medications with different biological mechanisms of action (Hori and Kunugi, 2013).

Dopamine dysfunction has been directly implicated in several other neurological disorders. For example, decreased dopamine synthesis has been correlated with
symptoms of Parkinson’s disorder, and the disorder is often treated using dopamine precursors such as L-DOPA (Cools, 2006). Consequently, individuals with Parkinson’s disease are at a heightened risk of developing depression, anxiety and apathy relative to the general population (Skorvanek et al, 2015). Additionally, agonizing D2 and D3 receptors using piripedit improves symptoms of post-operative apathy after therapeutic stimulation of the subthalamic nucleus (Thobois et al, 2013), suggesting they are a coupled side effect of inadequate dopaminergic functioning.

Several studies have also shown cerebrospinal fluid (CSF) levels of dopaminergic metabolite, ‘homovanillic acid’ (HVA), is scarce in patients with depression compared to healthy controls (Åsberg et al, 1984; Reddy et al, 1992; Virkkunen et al, 1995). While this does suggest biological involvement in the pathophysiology of depression, data exploring the relationship between scores on the Hamilton Depression Rating Scale (HAMD) and HVA CSF levels have conflicting reports (Kasa et al, 1982), (Mann et al, 2014). The research failed to find a relationship between CSF HVA and HAMD did demonstrate a positive correlation between HVA-CSF of depressed patients and physical symptoms of anxiety (Mann et al, 2014), which may suggest a more direct relationship between dopamine functioning and the anxiety-like symptoms of depression.

**Norepinephrine**

Norepinephrine (noradrenaline) is well known for its role in the fight or flight response. Primarily synthesized in the locus coeruleus (LC), this neurotransmitter shifts an individual from a dormant to an alerted state, with increases in arousal and overall performance. Post-mortem MDD patients demonstrated increased genetic expression of NMDA receptor subunit genes in pyramidal neurons located in the LC,
but not in the PFC. As NMDA is a glutamatergic receptor subtype, this finding suggests MDD patients have elevated norepinephrine and glutamate activity in the LC (Chandley et al., 2014), but perhaps connecting pathways may be disrupted and cause this hyperactivity to normalize at the PFC. Most MDD patients included in this study had committed suicide, and as such, it is unclear whether these differences are related to suicidal ideation, or the two key components of depression: depressed mood and anhedonia. Yet, others have reported findings juxtaposing this position. Magnetic resonance imaging (MRI) has shown LC is underactive in patients with depression (Shibata et al., 2007), and another post-mortem study has demonstrated reduced levels of norepinephrine transporters of the LC in patients with MDD (Klimek et al., 1997). Future research into the exact role of norepinephrine may help to isolate treatment options of deficiencies in this system.

Regulatory Neurotransmitters and Neuropeptides

Gamma-aminobutryic acid (GABA) Deficit

Gamma-aminobutryic acid (GABA) is the primary inhibitory system of the human brain, and is released by approximately one third of cortical neurons (Purves et al., 2001) (Petty, 1994). Two separate types of GABA receptors with different mechanistic properties are involved in its neuronal chemical signaling. First, GABA_A receptors are ionotropic, meaning they are closely coupled to ion channels, which open immediately upon GABAergic binding. Conversely, GABA_B receptors are metabotropic, meaning they are coupled to g-proteins, and involve the activation of secondary messengers to open ion channels. For this reason, the action of GABA_A binding works very rapidly, while GABA_B effects on neuronal hyperpolarization are relatively delayed. For in depth descriptions, the reader is encouraged to refer to an extensive review (Bormann, 2000). The GABAergic system plays a key role in
inhibitory processes, and malfunctioning of GABA\textsubscript{A} or GABA\textsubscript{B} binding can result in many functional impairments.

Studies of patients with MDD have demonstrated neurotransmission of GABA is impaired by a reduction of available GABA\textsubscript{A} receptors (Luscher \textit{et al}, 2011). There is also evidence suggesting GABA has a prominent role in hippocampal neurogenesis (Li \textit{et al}, 2009), and being treated with antidepressants increases neurogenesis in the hippocampus (Dranovsky and Hen, 2006). Additionally, hippocampal neurogenesis is a strong indicator of antidepressant response in humans (Santarelli \textit{et al}, 2003), supporting the hypothesis that GABA neurotransmission is one of the key biological changes responsible for reduced depressive symptoms (Croarkin \textit{et al}, 2011).

Due to its hyperpolarizing effects, increased GABA transmission is coupled with increased global functional connectivity (Fingelkurts \textit{et al}, 2004), suggesting the hyperactivity of regions involved in depression, such as the hypopituitary adrenal (HPA) axis, may be the result of insufficient GABAergic activity (Pariante and Lightman, 2008).

Studies have shown approximately 1/3 of patients with MDD have demonstrated lower plasma concentrations of GABA metabolites relative to healthy controls, and impaired GABA metabolism was indicative of increased symptom severity in patients with depression and suicidal ideation (Setoyama \textit{et al}, 2016). Research also indicates a small but highly significant relationship between cerebrospinal fluid (CSF) GABA levels and depression, with CSF GABA accounting for approximately 8\% of the variance in symptom severity. While this was a highly statistically significant finding, the limited ability of CSF GABA levels to predict depressive symptoms suggest it is one of several related biological mechanisms of depression.
Proton Magnetic Resonance Spectroscopy (H-MRS) has revealed low cortical concentrations of GABA in patients with MDD relative to healthy controls (Sanacora et al., 1999), a trend which normalizes after a course of ECT (Sanacora et al., 2003) or SSRI treatment (Sanacora et al., 2002). These investigations were confined to the occipital cortex due to technological limitations, and as such, interpretations of these findings should be made with caution. A more recent study using the same technology showed significantly lower GABA levels in the ACC of adolescents with MDD, (Gabbay et al., 2012), which supports the possibility that GABAergic functioning is impaired in regions both strongly and weakly associated with depression, suggesting decreased GABAergic metabolism may be a global phenomenon.

While this may be the case, detailed post-mortem research may tell a different story. Researchers investigating gene expression in different areas of the brain between people with and without MDD diagnoses who died by suicide and compared them to individuals who died by other causes without a history of psychiatric illness (Sequeira et al., 2009). These investigations revealed GABAergic and glutamatergic genetic expressions were indicators of suicidal behavior. Moreover, the highest number of suicide-specific differences were noted in the prefrontal cortex and hippocampus, suggesting these regulatory neurotransmitters play a role in suicidal ideation. It also indicates that, while global differences in gene expression are present globally, they are most prominent in areas involved in anhedonia.

**Brain-Derived Neurotrophic Factor**

Brain derived neurotrophic factor (BDNF), is a hormone involved in neurogenesis during fetal development (Aguado et al., 2003), synaptogenesis throughout the lifespan, and plays a role in learning and memory (Cunha et al., 2010). BDNF has been implicated in regulating the activity of glutamate, GABA, and serotonin through tertiary processes and activates genes involved in serotonin transportation. The
BDNF hypothesis of depression suggests impairment in BDNF functioning results in depression, a claim is supported by several studies. For instance the met allele of the BDNF Val66Met polymorphism is associated with increased BDNF concentrations in blood serum (Lang et al, 2009), and individuals with the Val/Met polymorphism are less likely to develop depression compared to the Val/Val genotype (Gatt et al, 2009). Additionally, patients with MDD tend to have lower plasma and serum levels of BDNF, a trend which partially normalizes after antidepressant therapy (Gervasoni et al, 2005).
1.3 Networks involved in Specific Symptoms of Depression

Reward Network and Anhedonia

Anhedonia has been described as a diminished interest or pleasure in once enjoyable activities, and is one of two symptoms required for a diagnosis of major depressive disorder (MDD) (Treadway and Zald, 2011). Anhedonia affects many individuals with treatment-resistant depression (TRD), and has been implicated in faulty reward circuitry, with certain regions exclusively related to the presence of anhedonia but not low mood (Bielczyk et al, 2015; Wacker et al, 2009). The ventromedial prefrontal cortex (vmPFC) has received attention for its involvement in hedonic processes, and includes portions of the anterior cingulate cortex (ACC), the orbitofrontal cortex (OFC) as well as the prefrontal cortex (PFC) (Treadway et al, 2011).

These regions have been shown to be involved in suicidal thoughts in patients with depression, and have strong connections to the ventral striatum in human brains, including the nucleus accumbens (NAcc), which is also involved in the reward circuit (Haber and Knutson, 2010). A wide variety of research suggests the brain regions involved in hedonic reward can be altered by different brain stimulation techniques (Bewernick et al, 2010; Downar et al, 2014), including electroconvulsive therapy (Ota et al, 2015).
Suicidal Ideation

Research has shown different pathophysiology exists between individuals with major depressive disorder with and without suicidal tendencies. While different post-mortem evaluations of glial cell counts did not differ between diagnoses of schizophrenia or depression, patients with either diagnosis who died by suicide had increases microgliosis in the DLPFC, ACC, and medial dorsal thalamus (MDT), suggesting suicidal ideation has biological underpinnings distinct from other features of MDD. (Steiner et al, 2008).

Supporting this finding, Monkul and colleagues found that female unipolar depressed patients with one or more suicide attempts in their lifetime had significantly smaller orbitofrontal grey (OFG) matter volume compared to healthy controls. Interestingly, they also exhibited increased right amygdala volume compared to unipolar patients with depression who have never attempted suicide (Monkul et al., 2007). It has been suggested that these abnormalities in the prefrontal cortex and amygdala cause dysfunctional arousal states and periods of diminished inhibition, predisposing patients to impulsive reactive behaviour such as attempting suicide.

1.4 Cellular and Network Mechanisms of Generalized and Partial Seizures

Overview of Seizures and MDD

Generalized seizures have been used to treat psychiatric disorders for decades, and using seizures to treat major depressive disorder (MDD) occurred before rigorous preclinical trials were required(Accornero, 1988). As such, there is limited
information about the biological mechanisms of action of convulsive therapies to date, but a growing body of evidence can help to elucidate these processes. A recent case study reported a 43-year old woman who developed epilepsy in her early 20’s and was prescribed antiepileptic drugs, developed (MDD) shortly thereafter (Weaver, 2009). After failing to respond to antidepressant medications, she intentionally stopped her anti-epileptic medication for 5 days and underwent a series of seizures. She continued to abruptly attenuate antiepileptic medications once a month for 5 days at a time, and effectively achieved remission of her depressive symptom (Weaver, 2009). For this woman and many other patients using ECT, seizures have helped mitigate debilitating symptoms of depression and restore functioning.

There has been debate as to whether a seizure is necessary to induce therapeutic response in patients with depression or whether the electrical stimulation itself is driving the patients’ response. However, it is known clinically that sub-convulsive stimulation is ineffective (Laidlaw et al, 2000), and titration sessions are not considered treatments. Additionally, prior to the development of ECT, Flurothyl inhalation and pentylenetetrazol induced seizures were used to treat depression in the absence of an electrical stimulus (Cooper and Fink, 2014). Together, this evidence suggest inherent characteristics of seizures may be a mechanism by which ECT exerts its effects. Therefore, knowledge of the biological mechanisms of seizures can help to elucidate the possible antidepressant mechanisms of action of convulsive therapies.
What is a Seizure?: An Overview of the Ictal EEG

Both naturally occurring and pharmalogically- or electromagnetically-induced seizures often involve abrupt onsets and terminations. Tonic clonic seizures (such as those induced by ECT) involve repetitive and synchronized spike and wave discharges. These seizures can remain in confined areas of the brain (partial seizures) or affect neuronal firing globally across the brain (generalized seizures) (Dominguez et al., 2005). A generalized seizure usually starts with a ‘recruitment phase’, where abnormal activity arising from a selective group of neurons sends signals to other neurons and an irregular pattern of excitatory discharges occur.

In the polyspike phase of a seizure, these intense high-frequency discharges begin to involve more and more brain matter, and the early seizure phase begins to involve a multitude of brain areas. Then, physical convulsions begin as the signal has reached the motor cortex and muscles throughout the body begin to fire. During the ‘spike-and-wave’, or ‘slow-wave phase’ of a seizure, these physical convulsions become more rhythmic and cease once activity in the motor cortex dissipates (Figure 1b). Rhythmic spike and wave EEG patterning reflect abrupt excitatory discharges followed by relative silencing of neuronal networks that are involved in the spiking activity. Many researchers believe these periods of silence are primarily due to GABAergic and other inhibitory processes, which will be reviewed in the following sections.
Inhibitory and Excitatory Circuitry of the Brain

Prior to reviewing the biochemistry of seizures in depth, it is important to consider typical neuronal processes in the absence of ictal activity. The brain primarily contains two types of neurons: 1) pyramidal/principle cells, which primarily form...
excitatory synapse on post-synaptic neurons, and 2) interneurons, which primarily form inhibitory synapses on pyramidal cells or other inhibitory neurons. These two neuron types form three subtypes of neuronal inhibitory configurations, that, when disrupted, are involved in the onset and/or continuation of seizures. 1) feed-forward inhibition involves interneurons sending inhibitory signals to a principal cell, thereby decreasing it’s firing rate. 2) lateral feedback inhibition occurs when two or more pyramidal cells are activated simultaneously, and interneurons that mediate more than one pyramidal cells, suppress activity of weaker, neighbouring pyramidal cells while the most depolarized cell fires an action potential. 3) feedback/recurrent inhibition occurs when the firing rate of the principal cell is heightened. The firing rate of the interneuron then increases, which decreases the frequency of the principle cell firing an action potential. This negative feedback loop is known as recurrent inhibition, and is an important loop system that prevents ictal activity in non-epileptic individuals in the absence of a stimulus.

Pyramidal cells in a brain structure that project to the network can activate interneurons along the way. Depending whether the interneurons inhibit the same projection neuron (feedback inhibition) or neighbouring pyramidal cells (feedforward inhibition), different regions of the cortex can experience a reduction in excitability. It is through these connections that inhibitory and excitatory signals are sent throughout the brain, and an electromagnetic stimulus can induce action potentials in these pathways to activate a multitude of brain areas.

Excitatory processes also play a role in modulating the brain’s neuronal firing. Changes to cells in a circuit can affect both neighboring and distant neurons. Excitatory axons make numerous connections along their projection pathway, and these excitatory axons can increase the excitability of the network of connected
neurons, causing increased firing rates in proximal and distal locations in the brain. As such, the way in which a network is organized in relation to other cells can greatly affect the excitability of neurons within and surrounding that network. It is important to consider these connections when thinking about brain stimulation, so as not to minimize the effect altered brain activity in one area has on distal brain locations.

Using Electromagnetically Induced Seizures to Treat Depression

Naturally occurring seizures can arise from a multitude of pathologies in various brain regions (Blumenfeld, 2005), making treatment targets in the epileptic brain difficult to localize. However, when utilizing electrically or magnetically induced seizures as a developing therapy, seizure activity can be initiated in a multitude of focal brain areas, which can help us target specific brain regions or networks involved in depression. A wide variety of research suggests the brain regions involved in depression can be altered by different brain stimulation techniques (Bewernick et al., 2010; Downar et al., 2014), including electroconvulsive therapy (Ota et al., 2015). The next section will review the use of electrically induced seizures to treat depression.

1.5 Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is the most effective form of treatment for patients with treatment-resistant major depression (TRD), with an estimated 50-70% of
patients achieving response (Coffey, 1993). The first clinical use of ECT to treat human psychiatric disorders began with Dr. Hugo Cerletti in 1938, who had been searching for a method of inducing seizures to treat schizophrenia, and was inspired after seeing pigs experience generalized seizures when electrocuted for butcher meat and went on to develop ECT. Shortly thereafter, treatment became widely approved for clinical use, and at that time, psychiatrists did not provide anesthesia or muscle relaxant to their patients, and many suffered neuromuscular defects and cardiac related death. It wouldn’t be for another 30 years that the use of anesthesia during treatment would be a viable option for patients undergoing ECT (Payne and Prudic, 2009). Additionally, ECT developed a poor reputation historically as it was sometimes used in psychiatric institutions as a method of punishing and inducing fear and blind obedience in inpatients. There is little wonder why electroconvulsive therapy developed the reputation of being an inhumane treatment, but it is not clear why this reputation has been so resistant to change with medical developments over the past 50-70 years, when other developed treatments have gained wide public acceptance.

Currently, electroconvulsive therapy is conducted under general anesthesia with a muscle relaxant and is most often administered to individuals who are capable of providing consent or substitute decision makers who approve of the treatment. Patients are asleep for the duration of the stimulation and are under general anesthesia for approximately 5 minutes. As such, they do not experience pain when stimulated or have residual musculoskeletal impairments because of treatment. However, when patients receive ECT, an electrical current is applied directly to the surface of the scalp, but it is shunted by the skull and cerebrospinal fluid, stimulating most cortical regions including those involved in memory (Rush and Driscoll, 1968). As a result, cognitive impairment is a common side effect. While the cognitive side
effects have been minimized in ECT by altering electrode placements and stimulus intensities, memory loss is still a very real risk for patients receiving treatment, especially at higher doses when administered bitemporally.

Due to the historical use and cognitive side effects of ECT and, a small percentage of individuals who may benefit from the intervention go on to have treatment despite its incredible efficacy (Hermann et al, 1995). As such, novel treatments eliminating the cognitive deficits of ECT and minimizing associated stigma are necessary to explore. To ensure the greatest chance of success, novel therapies should tap into our basic understanding of the biological underpinnings of depression. As ECT is the most effective form of treatment, and is one of the only convulsive therapies to date, it is important to understand its potential biological mechanisms of action to increase response rates and minimize cognitive side effects. Below we review some of the most widely accepted theories of ECT mechanisms of action.

1.6 Theories of Electroconvulsive Therapy

Historical Theories

Early investigators postulated that the application of electricity to the brain was responsible for ECT’s clinical benefits. However, it is now known that different electrode placements in ECT can result in vastly different response rates, despite having equal charge. Others suggested the stimulation of deep brain nuclei were responsible for its’ efficacy. However, the advent of novel techniques that do not directly stimulate ventral structures under the cortex suggest this stimulation, at the very least, cannot account for all the clinically beneficial effects of ECT. More novel theories suggest the electrical stimulus pathway in the brain controls the efficacy of
ECT as well as side effects, however, the difference between bilateral and unilateral ECT, involving different pathways, decrease in efficacy with decreased dose.

1.7 Current Theories of ECT Antidepressant Mechanism of Action

Vascular Theory

The medical use of electroconvulsive therapy predates requirements set out by Health Canada to explore a medical device safety and efficacy in three-stage clinical trials. Thus, many of the potential biological underpinnings of ECT have not yet been thoroughly elucidated. However, there are several theories gaining wide acceptance by the scientific community, including the vascular theory of depression.

This theory is based on the high comorbidity between depression and vascular diseases, such as hypertension, high blood pressure, and diabetes, and postulates depression arises from inflammation of the vasculature supplying the brain. Research is underway exploring the use of anti-inflammatory medications to treat TRD. Krishnan et al (2017) used MRI imaging to define cerebrovascular depression, and found that those with later onset depression were at an increased risk of developing vascular than non-vascular depression. These results also demonstrated individuals with vascular depression were more likely to have a family history of suicide, anhedonic symptoms and cognitive impairments than non-vascular depressed counterparts (Krishnan et al, 1997). Patients with late-onset depression are also known to respond very well to ECT (Mitchell and Subramaniam, 2005), suggesting these populations may overlap.
It is well established there is a stark increase in blood pressure and heart rate immediately after ECT (Mander et al, 1987), demonstrating the ability of ECT to acutely regulate cardiac functions. New research suggests ECT may have longer lasting effects on vascularity, providing a more direct link between neuro-inflammation and depression. One of such studies demonstrated that patients with depression have heightened levels of tumor necrosis factor (TNF), an inflammatory cytokine. This abnormality was normalized after a course of ECT (Hestad et al, 2003), providing evidence that ECT can mitigate the neuro-inflammation in depression.

More recently, similar research has demonstrated increased pro-inflammation cytokine –TNF-alpha, and ant-inflammation cytokine, IL-10, are significantly depleted in the TRD brain relative to healthy controls. Moreover, patients exhibit higher level of pro-inflammatory IFN-gamma and anti-inflammatory IL-4 cytokines at baseline, which both normalized over the course of ECT treatment. The results of this study were therefore conflicting, but authors suggest while some pro-inflammatory cytokines increase, anti-inflammatory cytokines also increase to maintain homeostasis. The exact mechanisms behind this phenomenon are unclear and may indicate a complex relationship between inflammation and depression (Zincir et al, 2016). The results of this study also failed to show a relationship between depression severity and serum levels of inflammatory cytokines, suggesting the altered neuroinflammatory biomarkers after ECT may be a mechanism secondary to ECTs therapeutic effects.

**Anticonvulsant Theory**

The risk of status epilepticus from ECT stimulations as well as organically induced in epileptic seizures suggest ictal activity can be maintained until neurons have poor oxygenation and cell death occurs. Status epilepticus can last for days before this happens, suggesting it is not the absence of excitatory inputs, but inhibitory
processes are necessary to stop ictal activity. Numerous reports of relationships between treatment outcome and the degree to which the seizure terminates have been linked to ECT efficacy (Azuma et al, 2007). Moreover, patients who experience an increase in the seizure threshold over treatment are more likely to respond to ECT compared to those with minimal threshold increases. This suggests that mechanisms behind ECTs effectiveness are related to these inhibitory effects of ECT which makes subsequent seizures more difficult to elicit. After a full course of ECT medication-free patients had decreased regional brain metabolism that was widespread, but particularly robust in the prefrontal, frontal, and parietal cortices (Nobler et al, 2001).

Patients receiving ECT experienced increased glucose metabolism of the diencephalon, amygdala, vermis and frontal, temporal and parietal cortices during the ECT-induced seizure. Some of these brain areas had depleted glucose metabolism immediately after ECT, including the anterior cingulate gyrus and medial prefrontal cortex, two brain regions strongly involved in depression (Takano et al, 2007). Additionally, those who responded to ECT demonstrated larger reductions in brain oscillation frequency at rest post-treatment. Taken together, these studies suggest ECT plays a key role in increasing inhibitory processes.

1.8 Magnetic Seizure Therapy

Overview

Another form of convulsive therapy, Magnetic Seizure Therapy (MST), is currently under investigational use as an alternative to ECT with a putatively superior cognitive adverse effect profile (Moscrip et al, 2006). MST involves the application of high intensity repetitive magnetic field pulses that penetrate the cortex unimpeded and create a secondary electric field to induce a seizure(Lee et al, 2014). Due to
the properties of magnetic fields, direct stimulation is limited to superficial regions of the brain in most coil configurations (Deng et al, 2011). However, utilizing a twin coil montage allows for a maximum field strength to be summated in between the two coils, allowing for deeper regions of the brain to be stimulated in a focal manner (Deng et al, 2013b). Previous trials investigating MST as a treatment for treatment-resistant depression (TRD) have applied stimulation to the vertex (Kayser et al, 2011) (Kayser et al., 2011) and to the prefrontal cortex (Lisanby et al, 2003b). When stimulating the prefrontal cortex with a twin-coil, the maximum summated e-field strength is under Fz per the 10-20 system, with a much lower induced field in medial temporal structures (e.g., anterior hippocampus) linked to episodic memory function.

As such, MST has the potential to stimulate brain regions involved in depression while sparing structures involved in the cognitive adverse effects of ECT. Therefore, MST can be used to stimulate brain regions in the reward circuit and induce neuroplastic changes, and may be responsible for the therapeutic benefit of frontal MST in patients with TRD.

**Overview of Device Capacities: Four Generations**

Early explorations of MST were conducted using a standard TMS device known as the Magstim Super Rapid Stimulator. This device was paired with a figure-of-eight

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coil and generated a magnetic field of 1.8 tesla. Further developments by Magstim in collaboration with early investigators permitted the development of a more intense device. The second generation device, known as the Custom Rapid stimulator, generated a 40% greater output than the previous device, and allowed for 6.3 second stimulations of 40 Hz at 100% output intensity. While the exact generated magnetic field remains unpublished, the generated magnetic field is believed to be approximately 2-2.5 T at the surface of the coil. The third generation device came into research practice in approximately 2008, and was equipped to emit 100 Hz for 10 seconds, with 1.2 T generated at the coil. While this device permitted faster frequency stimulation trains and total number of pulses, it was also approximately half the intensity of previous devices. As such, its therapeutic benefit was minimized. MagVenture developed the 4th generation of MST devices which was paired with the twin coil, which had increased windings and ability to generate larger magnetic fields at the surface of the coil. Together, this pair was capable of inducing 2.75 tesla magnetic fields at the surface of each coil, and the field was strongest at the summation point of the coils. Moreover, the space in between the two coils allowed for flexibility of localizing target sites more than the theta-stimulator-coupled double-cone coil. Whilst this device can stimulate at a frequency of up to 250 Hz, there is a stark drop off in output of the coil, meaning the generated magnetic field is weaker than the advertised coil intensity at higher frequencies (Figure 2). In some cases, this roll off intensity is so prominent, the device intensity is lower than all previously explored devices. Indeed, MST device development is still in its infancy, and there are still many technological advancements needed to truly determine the best method of stimulation.

**Early Explorations of MST**

Transcranial magnetic stimulation was first used in neuroscience research as a method of studying the function of the motor cortex by evaluating its impact on the related muscles using electromyography, but was later adapted for treatment in
psychiatric disorders. Early reports of repetitive TMS (rTMS) for treatment resistant depression had favourable outcomes (George et al., 1995). However within a year of investigations into safety and clinical outcome, 7 accidental seizures were reported to be evoked using rTMS (Wassermann, 1998). This became a growing safety concern for the use of rTMS to treat depression and safety regulations were put in place to minimize the risk of seizures. Although it was believed to be an adverse event, researchers studying electroconvulsive therapy in depression saw it as an opportunity to induce focal seizures with hopes of minimizing cognitive side effects.

**First and Second Generation MST Devices: Proof-of-Concept**

**Magnetically Induced Seizures**

The first clinical trials investigating intentional seizure induction using rTMS began in 2000. Investigations in non-human primates began using high-frequency, high-intensity rTMS emissions from the standard rTMS device, Magsttim Rapid Stimulator, which allowed stimulations of 10 seconds at 25 Hz frequency (Lisanby et al., 2001a). Unfortunately, original technological device did not reliably induce seizures in all sessions due to device limitations, and novel models with increased electrical capacities were needed. As such, innovations were made to the Magsttim Rapid Stimulator to permit 40 Hz stimulations up to 6.3 seconds, to a maximum 252 pulses, and attempts continued in non-human primates (NHPs) with this device (Lisanby et al., 2001a). Although the maximum number of pulses delivered did not significantly increase with the new device, the amplitude of the coil current was 40% stronger at 100% intensity, and therefore successfully induced seizures in non-human primates. In fact, only 90% intensity was required for seizure induction.

Once seizures were reliably induced in monkeys, a further human case study investigated the use of this novel device for seizure inductions in a 20 year old
female with treatment-resistant depression (Lisanby et al, 2001b). The patient underwent 4 sessions of high-frequency, high-intensity rTMS with the goal of inducing therapeutic seizures, followed by ECT sessions. Sessions were administered 3 times a week similar to the standard ECT delivery frequency protocol. The first treatment administered the maximum output of the device, which successfully induced a seizure with 252 pulses, delivered in a 6.3 second train at 40 Hz MST. The visual seizure lasted 112 seconds, and the time to reorientation of this session was 23 minutes. This reorientation time was comparable to typical reorientation times seen in ECT. Due to the long seizure length and time to reorientation, it was suspected that lower doses of MST could be used to evoke seizures in humans with the Custom Rapid device.

The subsequent treatment session was titrated, first applying 2 seconds of 40 Hz, followed by a 4 second stimulation at the same frequency when the first stimulation failed to induce a seizure. The second stimulation lead to an eighty-second seizure. Again, this seizure induced a very long reorientation time of 30 minutes, with a total of 240 pulses applied over the treatment session. When authors were made aware of the pro-convulsant properties of anesthesia (Moore et al, 1994), a switch from etomidate to thiopental anesthesia occurred to ensure seizure induction was due to the magnetic stimulation alone.

For the third treatment’s session first titration, authors switched to prefrontal cortex stimulation to determine if seizures could be induced in this manner, with the following parameters: 126 pulses, figure-of-eight coil, 20 Hz for 6.3 seconds. When seizure induction failed, 136 seconds later, authors delivered 40 Hz stimulation to the double-cone coil to the vertex at 70% intensity and pulse width of 0.5 ms with 180 pulses. This was done to match the total applied charge of the last stimulus to
induce a seizure, as widening the pulse width increases the brain’s electrical exposure and compensate for the reduced output intensity (Kawashima et al, 2014).

The second titrated session induced a seizure and resulted in marked reduction in seizure duration at 44 seconds and the reorientation time decreased to 8 minutes. The fourth and final treatment session maintained the parameters of the previous treatment and induced a seizure without pre-stimulation to the prefrontal cortex. This seizure lasted 30 seconds long, which is 2/3 of the duration of the previous treatment. Over the course of 4 treatments, the patient showed a reduction in the HAMD from 20 to 14 points. According to recent reports (Lin et al, 2016), 3 sessions of ECT reduces depressive symptoms by 40% on average, suggesting MST is not only a feasible manner of seizure induction, but may reduce symptoms of depression at similar rates to ECT.

Indeed, the alterations in a number of treatment parameters for the third and fourth sessions of MST— namely pulse width, intensity, pre-stimulation to the prefrontal cortex, train duration, and switching anesthesia — makes it difficult to isolate the parameters were responsible for the decreased orientation time and seizure activity. Still, this was the served as proof-of-concept that seizures could be elicited in humans using repetitive magnetic stimulation, and suggested proceeding to multi-patient pilot studies were ethically sound and scientifically justified.

Small Pilot Investigation in TRD

The first randomized pilot study of MST studied 10 patients with TRD to investigate the safety and side effect profile of MST (Lisanby et al, 2003a). During the first and second session, each patient’s seizure threshold for ECT and MST were collected in a counter-balanced manner. The next 2 treatment sessions applied MST or ECT at 2.5 times the seizure threshold. The study reported significantly fewer subjective
side effects and faster recovery of orientation compared to those treated with ECT. Moreover, the MST treated group performed significantly better on tests of attention, retrograde amnesia and category fluency, suggesting MST is a viable alternative to reduce cognitive side effects. As only 2 treatments were given, this study did not investigate long-term side effects or the efficacy of MST in this patient sample. Over a decade later, further technological advancements coupled with investigations underpinning the biological mechanisms of action have provided insights into the optimization of MST for the treatment of depression.

1.9 Studies in MST: Third and Fourth Generation Devices

Efficacy

In 2015, Kayser and colleagues completed a study of MST treatment effects incorporating a large, in depth clinical, cognitive and neurological testing battery (Kayser et al, 2015). Using the MagPro MagVenture MST stimulator coupled with the twin coil placed over the vertex, the group delivered 12 treatment sessions twice a week to 26 patients with TRD. These stimulations were delivered at a frequency of 100 Hz and 100% output intensity of the device. On the first session, titrations were given in 50 pulse increments until the stimulus induced a motor seizure greater or equal to 10 seconds. The subsequent stimulations were performed at 2.5 seizure threshold by increasing the duration of the stimulus to 2.5 longer than that required to induce a seizure, to a maximum of 10-seconds. This sample demonstrated extremely high response rates relative to other clinical trials evaluating MST efficacy, with response and remission rates of the patient sample approaching 70% and 46% respectively.
Other MST treatment outcome studies provided a higher number of treatment sessions despite presenting lower rates of response in their sample. A small pilot study evaluating the efficacy of MST with the same device, coil, frequency and vertex position, but with stimulations of up to 10 seconds (1000 pulses) and 18 treatment sessions (Fitzgerald et al, 2013). Instead of providing titrating at 50 pulse intervals, MST seizure threshold was determined by titrations of 200 pulses at increasing equal intervals until a seizure was elicited. Subsequent seizures were produced by stimulations 4 seconds longer than the seizure durations, and if motor seizures lasted less than 15 seconds, train lengths were increased by 2 seconds at a time to a maximum of 10 seconds. This sample demonstrated reduction in several measures of depression as well as the brief psychiatric rating scale (BPRS). response and remission rates of the sample were 39% and 15% respectively, which is much lower than the previously discussed finding (Kayser et al, 2015).

All individuals in the sample demonstrated reduction in anxiety symptoms across the treatment course, although responders had significantly larger reductions in anxiety symptoms relative to non-responders. Other reports have suggested MST may directly affect brain processes involved in suicidal ideation (Sun et al, 2016), but this measure was not evaluated in this study. A large-scale clinical trial evaluated predictors of anxious-depression and found that higher rates of suicidal ideation were among these participants than those with other types of depression (Fava et al, 2004). It is possible these two research outcomes are linked, however further work in patients with anxious subtype of depression compared to other forms of depression should be conducted to determine whether MST treatment outcome is better for specific indications of depression, and additional measures evaluating suicidal ideation are also warranted.

Additionally, this paper included 8 individuals with bipolar II and one individual with bipolar I currently in an episode of depression. Previous research has demonstrated
decreased treatment sessions for response of bipolar patients with depression compared to patients with unipolar depression (Daly et al, 2001), and as such, this may provide one explanation for the heightened response rates after just 12 treatments. However, the authors did not disclose the diagnostic information of the responders, non-responders and remitters, which may have provided useful information about the specific indications and their likelihood of responding to MST.
1.10 Studies of Physiological Effects of MST

Non-Human Primate Models: Intracranial EEG

Early investigations used intracranial electrodes to record the ictal electrical activity inside the brain of non-human primates. The group treated NHPs with ECS or MST using a within-subjects design and measured the spread of ictal activity (Lisanby et al, 2003b).

In the ECS treatment sessions, when stimulating over the right frontal cortex, there was widespread activation during the ictal period. Seizures propagated to a multitude of distal brain areas, including the contralateral frontal area, deep brain structures and distal regions of the parieto-occipital junction. Upon seizure termination, ECS recordings demonstrated a pronounced shift from high amplitude, regular ictal activity to an abrupt attenuation of cerebral activation upon seizure termination.

In contrast, MST produced weaker excitation over the seizure’s duration, and activity was primarily limited to the site of stimulation. Authors concluded that, due to the low level of excitation evoked in regional electrodes, the hippocampus is unlikely to be largely affected by seizure activity in MST, if at all. Moreover, the transition from ictal to post-ictal activity was subtle, with similar activation patterns across both time periods, demonstrated by robust differences in post-ictal neural activation. Spectral analyses of the post-ictal period revealed stronger activation in the alpha, beta and
delta ranges in ECS, but similar theta activity as compared to MST (Lisanby et al, 2003b).

**Seizure characteristics**

The first pilot study of MST side effects was also the first to evaluate the visual EEG characteristics (Lisanby et al, 2003a). Compared to the ECT sample, patients treated with MST had shorter EEG seizure durations, lower ictal amplitude, and less prominent post-ictal suppression. While this study was limited by the small sample size and few within-subjects seizures analyzed, this paper described aspects of the ictal EEG that have been reproduced by other authors.

A small patient sample (n=13) received up to 18 treatments of MST (Fitzgerald et al, 2013). While quantitative analyses on measures of seizure adequacy were not performed, the authors noted qualitative differences in seizure patterns in MST compared to stereotypical ECT ictal waveforms. Moreover, they noted that, while some MST seizures conformed to typical seizure patterning seen in ECT, this was not always apparent. They suggested post-ictal suppression is not as prominent in MST, and they did not see an obvious visible relationship between clinical response and the MST seizure pattern. Another group had trends towards less robust post-ictal suppression and ictal expression of MST compared to ECT seizures, although they did not find any significant differences between the two groups (Kayser et al, 2013). However, it should be noted patients included in this study did not respond to MST or subsequent treatment with ECT, which is perhaps more suggestive that treatment non-responders have similar characteristics across the two treatment types.

A study evaluated EEG seizure characteristics in a sample of 26 patients and found that no seizure outcome measures distinguished responders from non-responders,
nor non-responders from individuals who relapsed (Kayser et al, 2015). Of particular interest, these two studies did not identify a relationship between post-ictal suppression and clinical outcome, when this measure is arguably the strongest identifier of a high quality ECT seizure (Mayur, 2006). However, more robust excitability under the site of stimulation, and using distal EEG recordings may dampen the differences in ECT and MST induced seizures.

**Simulation Studies**

Estimated electric field neural activation thresholds were initially presented by Deng and colleagues, who showed the average electric field strength required to stimulate the majority of neurons in a brain area 0.25 V/cm at 0.3 ms pulse width for ultra-brief ECT and MST was likely and 0.64 V/cm at 0.4ms pulse width (Deng et al, 2011). These estimates suggest ECT pulses directly stimulate a greater brain volume relative to MST, with up to 98% of the brain’s neurons membrane potential being directly altered by the electrical stimulation.

The paper also identified differences in the focality and strength of the electric field induced by MST can be modified by changing the shape of the coil. The ‘double-cone’ coil demonstrated superior focality relative to the circular and cap coils (Figure 4d).

Moreover, ECT paradigms associated with milder cognitive effect profiles demonstrated comparable focality to circular and cap coil MST pulses. This finding suggests it may be the effects of stimulating brain tissue to depolarize almost all neurons, opposed to stimulating 50% or more of neurons in a brain area, that is responsible for adverse cognitive side effects. High-strength e-field brain area differed only slightly from the brain area affected by the low-strength e-field of the
double cone coil, demonstrating that almost all brain tissue directly affected by the stimulation experiences high-strength electric fields.

Subsequent research conducted in realistic head models suggested the Magstim circular coil produced an electric field of 0.19 V/cm, suggesting the stimulation is only 0.3 times the seizure threshold. In contrast, bitemporal ECT produced stimulations approximately 3.4 times the seizure threshold, suggesting overstimulation (Lee et al, 2014).

Figure 2: Electric Field Strength and Focality Differences Between MST Coils and ECT Paradigms. Adapted with permission from Deng et al. (2011)
MST and the Treatment of Other Indications

Once the safety and feasibility of MST had been established in patients with treatment-resistant depression, researchers expanded testing to patients with more complicated indications. In one case study, a 66 year old woman with a five-year long episode of refractory treatment-resistant depression which began when she was 17. The woman had a complex history of comorbid psychiatric disorders, including anorexia and obsessive compulsive disorder (OCD), which made her hesitant to taking medications that may cause weight gain. Using the custom rapid stimulator, the patient was delivered vertex MST which lead to a drop on the HAMD-21 from 33 to 6 points over the course of 12 treatment sessions. Cognitive functions remained unaffected, and baseline BOLD response (Blood Oxygenation Level Dependent signal) increased in the left fronto-parietal region and the brainstem. The increased BOLD response under the site of stimulation suggests changing the site of stimulation may be used to modify the activity of under-active brain regions involved in depression. It has also been suggested that MST may be able to decrease overactive brain regions as well by modifying the frequency of stimulation (Lisanby et al, 2003b). However, little research has been conducted to evaluate the effects of altering frequency and its effects on response and activity of different regional targets.

Further explorations of MST used for bipolar disorder were evaluated and found to be helpful in the treatment of bipolar depression in a case report (Noda et al, 2014). In contrast, another report of several cases in bipolar disorder revealed that MST could trigger mania (Noda et al, 2015).
Pretreating with rTMS to Lower MST Seizure Threshold

Alterations in these parameters may help us form some hypotheses about the effectiveness of altering certain treatment parameters to cause seizure induction (Lisanby et al., 2001a). It may be that pre-stimulating the prefrontal cortex prior to seizure induction lowers the seizure threshold, increasing the degree to which the stimulation exceeds the seizure threshold, thereby increasing seizure duration. This observation was also previously made in ECT stimulations, where multiple monitored ECT (MMECT), a form of ECT where sessions are applied in the same day, subsequent sessions required reduced charge to elicit a seizure, but when ECT sessions were spread apart, subsequent treatment sessions had the opposite effect (Roemer et al., 1990). It should be highlighted that this pre-stimulation was subconvulsive yet also caused a decrease in seizure threshold. For patients with high seizure thresholds, pre stimulation with an rTMS train may result in lower seizure thresholds in MST, which can reduce the need for high intensity stimulation. As such, the limitations of current device restrictions may be minimized.

1.11 Stimulation Waveforms in ECT and MST

ECT has been used for many decades, and most optimal parameters have been elucidated. Initial therapeutic interventions used sinusoidal stimulation waveforms, which exposes the brain under constant changing electrical current for the duration of the stimulation. However, by the 1940’s brief-pulse waveforms were being explored as a potential alternative (Kellner et al., 2010), which reduced the output to brief 0.5-1.5 ms stimulations with periods of electrical silence, known as inter-stimulus intervals (Figure 4). Rectangular pulse shapes are more energy conserving over the stimulus train, as the total time of the electrical output is limited to three
thousandths of a second per pulse. This results in a 2-fold decrease in the brain’s exposure to electrical stimulation.

Figure 4: This figure displays different ECT stimulus waveforms with the same frequency. Stimulus A has the same shape as MST waveforms possible with current devices, and is a cosine pulse.

In 1986, a randomized control trial comparing the efficacy and cognitive effects of sine wave and brief pulse ECT in bilateral and unilateral electrode positions revealed that sinusoidal waveforms cause drastically more cognitive impairment than square pulse waveforms within the first hour after treatment, however cognitive impairment differences between the two treatments diminished after an hour (Squire and Zouzounis, 1986). As patients often complain of long lasting autobiographical and episodic memory impairment around the time of treatment (Calev et al, 1995; Fraser et al, 2008), new parameters of ECT were still required to minimize these adverse effects.
The most cognitively sparing form of ECT applies a train of very short (<0.3 ms) electric pulses to the brain to induce a seizure. This method, known as right-unilateral ultra-brief ECT, has demonstrated both superior cognitive side effects and efficacy compared to brief-pulse durations and bilateral configurations (Sackeim et al, 2008), but some clinicians have been concerned about a possible slower time to recovery response in ultra-brief ECT despite equal efficacy (Loo et al, 2012). However, until randomized control trial data is collected on the time to recovery, right unilateral ultra-brief ECT is currently considered the preferred form of ECT in modern brain stimulation to minimize cognitive side effects.

Although many advances have been made to optimize ECT, there is still a risk of memory impairment. With the advent of MST, researchers hope to eliminate this potential for memory impairment, although it is in exploratory stages and optimal parameters have not yet been elucidated. The MST waveform is very similar to those initially used in ECT, and has a dampened cosine waveform (McClintock et al, 2011) with a pulse duration very similar to ultra-brief pulse ECT (370 μs) (MagPro MST User Manual UK version, software v.7.0.1RC8, Magstim, Tonica Elektronik). However, ultra-brief ECT uses bidirectional current with rectangular pulses, compared to the biphasic sinusoidal waveforms of MST pulses. This means a bidirectional ECT stimulus alternates anode and cathodes with each pulse, with the current first flowing in one direction, then in the opposite direction with the subsequent pulse. One ‘cycle’ of a bidirectional current consists of two pulses, whereas the ‘cycle’ of a unidirectional current is only one pulse. As frequency is calculated in cycles per second opposed to pulses per second, bidirectional stimulations have twice the number of pulses per train at the same frequency as
unidirectional stimulations. Therefore, the number of absolute pulses in addition to frequency are important parameters to control for across stimulation types.

In MST, however, a single sinusoidal pulse consists of two directions, meaning the cycles per second as well as the inter-stimulus intervals, are not equal to ECT at the same frequency. Moreover, a changing magnetic field capable of inducing a secondary electrical field large enough to evoke a seizure comes at an extremely high energetic demand, and technological limitations make monophasic waveforms next to impossible for current MST devices. This is because biphasic waveforms are induced using existing current in the coil, whereas monophasic waveforms must generate new electrical outputs with every stimulation. With present devices, using a monophasic waveform would result in approximately 50% dampened amplitude intensity comparable to non-convulsive TMS devices, and patients may be at a heightened risk for a missed seizure.

Finally, Faraday’s law of induction states that a secondary electric field can be induced using a changing magnetic field (López-Ramos et al, 2008). If the current stays stagnant for a period, as it would should there be inter-stimulus intervals with MST, the induced electrical field would instantly dissipate and would not likely cause convulsions. As such, there are very limited ways to manipulate the waveform of MST with current devices. Therefore, optimizing other parameters of stimulation may be the best way to increase the cost-to-benefit ratio of MST with current technical limitations.

Although most parameters of the waveform cannot be modified, research has shown altering the direction of the first section of the biphasic waveform in a single TMS pulse as well as the pulse width can create different neuronal responses. It is difficult to alter the pulse width of MST limited due to the energetic demand and issues with
coil overheating. Although the pulse width can be shortened, the rise of the stimulation can only occur as fast as the magnetic current can be induced. Due to the limitations on the time to highest stimulus amplitude, this shortened pulse width causes decreased electrical amplitude in the coil as the intensity cannot fully rise, and as such, a weaker magnetic field is generated.

However, altering the first current direction of a biphasic waveform can be done either by turning the coil upside down to generate opposing current directions. In this way, one can change the neuronal firing properties and alter the electrical field distributions inside the brain. For instance, using single-pulse TMS, Kammer and colleagues found that having the first biphasic waveform pulse run anterior to posteriorly was significantly better at inducing action potentials than when it moves posterior to anteriorly (Kammer et al, 2001). Moreover, Deng et al. created a stimulation study of 50 coil types, and demonstrated that the same 70 mm butterfly Magstim coil could induce very different electrical field properties by altering the direction of the current (Deng et al, 2013b). The first current running anterior-posteriorly induced a far more focal, but less intense electrical field than the one running posterior-to-anterior, which created a very strong electrical field in much deeper brain structures while leaving the area closest to the coil at a relatively low electrical field strength.

Prefrontal vs. Vertex Targets of Stimulation

Due to the involvement of the prefrontal cortex in depression, it would seem like an optimal location for targeted treatment. Early attempts were made to target the prefrontal cortex as it is a primary region of interest in depression (Kirov et al, 2008). Using third generation theta stimulator device, only 3 out of 7 stimulations resulted in successful seizure induction at the prefrontal cortex, and it was noted that seizure thresholds were much lower over the vertex due to its close proximity to the motor
cortex (Kirov et al, 2008). While these investigations predated novel technological developments allowing for increased electrical capacity, vertex stimulation has continued to be the standard site of stimulation for MST despite doubling the potential output intensity with the new MST device. Only one publication to date has evaluated prefrontal MST stimulation using the MagVenture MagPro, and demonstrated that baseline measures of GABAergic functioning predicted reductions in suicidal ideation after MST intervention. This paper suggests frontal MST is useful for patients with suicidal thoughts, however, the outcomes of frontal MST were not reported, and comparisons between stimulation target locations have not been systematically evaluated. As such, future research is needed to compare the two primary targets of stimulation.

**Altering Parameters of ECT**

Different parameters of electromagnetic stimulation and how they affect neuronal stimulation and outcome have been summarized. For instance, sine-wave pulse shapes in ECT induce far greater cognitive deficits than those with square pulse shapes, while being no more effective at reducing symptoms of depression (Squire et al, 1986). Similarly, the pulse duration can also alter the effectiveness of ECT. RUL Ultra-brief pulse ECT (using 0.3 ms stimulation) has demonstrated a superior cognitive side effect profile (Kim et al, 2007) but slower rates of response compared to standard RUL brief-pulse ECT (Loo et al, 2008). As well, altering the pulse width of a stimulus, such as shortening the pulse width from 0.5 to 0.3 ms (changing the stimulation from brief- to ultra-brief- ECT), requires an adjustment in stimulus duration to compensate for the decreased brain volume directly stimulated, demonstrating the issues of dosing metric comparisons across treatment types. Taken together, these results support the notion that altering any of the stimulus
parameters can cause a wide disparity of clinical interpreting the cumulative dosing metric.

Moreover, titrating a stimulation by frequency requires a higher stimulus charge to elicit a seizure than when titrating by stimulus duration (Devanand et al., 1998), and ultra-brief ECT stimulations require higher frequencies to induce a seizure than brief-pulse stimulations (Andrade, 2001). Additionally, Deng and colleagues have demonstrated the electrical fields induced by different stimulus amplitudes can have very different biological effects on the brain. In a simulation study, they demonstrated altering the treatment amplitude and electrode position can change the depth and spread of the electric field distribution in a simulated spherical model of the brain (Deng et al., 2013a). Shortening the pulse width has been found to lower the amount of neural membrane depolarized by each pulse in ECT (Deng et al., 2011). As such, decreasing pulse width, such as with brief- and ultra-brief pulse ECT eliminates many of the common side effects in memory. They also found that, while anatomical variability predominantly affected the ECT treated brain, MST induced electric fields were susceptible to differences in head diameter across patients while remaining insensitive to other variations in anatomy (Deng et al., 2013).

1.12 Using Seizure Characteristics in Convulsive Brain Stimulation Therapies

Monitoring ECT Seizures Throughout History

The Electroencephalogram (EEG) is a tool that measures the frequency and amplitude of electrical signals on the surface of the skull, and displays these cerebral patterns over time. EEG is commonly used during convulsive brain stimulation to record brain activity during and post seizure to confirm absence of
prolonged seizures and that fundamental seizure requirements have been met. For a motor seizure to be considered ‘adequate’, it must last a minimum of 15 seconds, as per the Royal College of Psychiatrists’ guidelines (Scott, 2005).

‘The cuff technique’ is a method of monitoring the motor duration of an ECT-induced seizure when muscle relaxants have been administered. This method involves isolating an extremity prior to administering the muscle relaxant so the physical seizure can be more accurately monitored. Although many ECT clinics use the cuff technique, it is not an enforced method of standardized practice. The cuff method alone does not completely prevent the muscle relaxant from entering the isolated extremity, and as such, adequate seizures may be incorrectly reported as shortened or missed seizures. Consequently, approximately 5.2% of patients who display no motor seizure have a detectable seizure on the EEG, with some of such patients even experiencing prolonged EEG seizures (Girish et al, 2002). While seemingly minute, solely using the cuff method of seizure duration quantification can be very dangerous as patients experiencing prolonged cerebral seizures are at a heightened risk of post-ictal confusion, long term memory impairments, and entering a condition known as ‘status epilepticus’ (Benbow et al, 2003; Girish et al, 2002; Scott and Riddle, 1989) that, when left untreated, can lead to sudden death (Cherian and Thomas, 2009).

The cuff technique alone is therefore a precarious and inappropriate method of quantifying seizure duration, especially for patients with unknown seizure thresholds. This is because standard practice guidelines recommend increasing the dose of the electrical stimulation when seizures are short presenting, and if seizures are mistakenly quantified as inadequate, physicians may stimulate to high over the
seizure threshold and increase memory impairment. Shortened or missed seizures are also cause for concern, as the effectiveness of ECT is highly dependent on the extent to which the stimulus dose exceeds the seizure threshold (Sackeim et al, 1993; Sackeim et al, 2000). As such, the minimum adequate motor seizure guidelines under the cuff technique cannot be lowered to adjust for this difference as its’ effects on the motor seizure can vary across patients and treatment sessions. As such, confirming seizure duration with additional methods can increase the reliability of seizure duration information, and therefore minimize risk in clinical practice.

Monitoring the ECT seizure duration is a relatively new problem, as early investigations of ECT did not incorporate muscle relaxants or anesthesia into clinical practice. It was believed there was no need to monitor the EEG during treatment as sufficient information about seizure adequacy could be obtained by the physical seizure alone. However, with the advent of ‘modified ECT’ (a practice that incorporated muscle relaxant administration prior to treatment), and the physical seizure became more difficult to observe, new methods of seizure monitoring warranted elucidation. Electroencephalography was introduced as a possible method of monitoring the seizure duration shortly after modified ECT came into effect (Furman et al, 1957).

The first suggestion that the EEG could be related to therapeutic effectiveness was proposed in 1951 based on EEG changes that occurred after ECT administration. While an important step in scientific discovery, this study only evaluated the use of pre-ECT and post-ECT EEG analyses, without examining the inter-ictal EEG (Roth, 1951). It wouldn’t be for another 6 years before EEG monitoring during the ECT seizure would be proposed as a method of evaluating seizure adequacy during ECT.
procedures (Furman et al., 1957). At the time, seizure characteristics were grouped only as ‘grand-mal’ and ‘non-grand mal’ EEG patterns, and demonstrated grand mal patterns were better at inducing physical contractions as monitored by the cuff technique, and it was a more reliable metric for modified ECT use than methods of evaluating the physical seizure.

The first descriptions of inter-ictal EEG patterns in ECT were defined almost a decade later, when it was noted that ECT-induced seizures were followed by a brief period of electrical silence, now known as ‘post-ictal suppression’ (Blachly and Gowing, 1966). They noted older patients had poorer seizure quality that “broke down faster” than younger patients, and was thus the first scientific report of worsened EEG seizures with increased age. Finally, they examined the seizure durations of treatments administered 2-3 times a week and compared them to seizures induced by multiple monitored ECT treatments (MMECT), a practice of performing multiple ECT treatment sessions under a single period of anesthesia, and is rarely used in modern ECT practice due to heightened post-ictal confusion (Roemer et al., 1990)(Roemer, Dubin et al. 1990). The MMECT elicited seizures performed at six-minute intervals induced longer seizure durations with each subsequent stimulation in a single treatment session, but described decreased seizure durations when stimulations were given 2-3 times per week (Blachly et al., 1966). Later research would describe this phenomenon as a representation of an increase seizure threshold (Coffey et al., 1995), whereby a patient requires an increased stimulus intensity to match the same electric dose in previous treatment sessions.

An early study evaluated the effectiveness of total seizure duration over an ECT treatment course and found a significant relationship with EEG seizure duration and
treatment response (Maletzky, 1978). This paper reported the relationship between total seizure duration across treatments, and suggested 750 seconds of total seizure activity over an ECT course would produce an adequate treatment response.

Maletzky also suggested these total EEG durations were more informative than the total number of treatments in predicting whether a patient would respond to a course of ECT. The first investigation for a single treatment duration requirement is credited to Dr. Max Fink, who disclosed his method of observing treatment adequacy in ECT via the monitored cuff technique (Fink and Johnson, 1982). This group reported their process of restimulating a patient should a physical seizure last less than 25 seconds, although this cut off point has been lowered to 15 seconds according to present day ECT guidelines.

Mandated ictal EEG recording has been incorporated into the Royal College of Psychiatrists’ ECT guidelines, requiring EEG equipment be available at every ECT clinic in the UK. EEG duration guidelines have also been set, with an adequate seizure lasting 25 seconds or longer (Scott, 2005). While these standard practice guidelines are imminent for patient safety, research has shown they can be used to investigate the characteristics of ECT-induced seizure to further elucidate the best parameters of stimulation.

Due to the focused research on seizure duration and the replicated relationship between duration and treatment outcome, for decades the length of the seizure was the primary variable evaluated to determine seizure adequacy. As additional qualitative methods of evaluating an ECT-induced seizure came to light, these methods were explored as possible indicators of therapeutic effectiveness. For the past two decades, characteristics of seizure quality have been intensely explored, and researchers have found characteristics relate to more efficacious forms of brain stimulation techniques. The most commonly cited methods of analyzing ictal EEG
recordings comes from two principle texts. The first, a book chapter by Weiner and Krystal (1993), introduced a set of instructions for EEG monitoring of seizures during ECT, which included a guide for rating global seizure strength (regularity) (Coffey, 1993) (Figure 5).

Figure 5: Global Seizure Strength Diagram. A rating of 0 indicates no seizure activity, while a rating of 6 indicates strong seizure activity. Figure adapted with permission from: Weiner and Krystal, 1993. Book Chapter 6: EEG Monitoring of ECT Seizures. In: The Clinical Science of Electroconvulsive Therapy, Editor: C.E. Coffey. (1993).

Nobler et al (1993) investigated the relationship between stimulus intensity and electrode placement on the characteristics of the seizure (Nobler et al, 1993). These included instructions on how to rate symmetry and global seizure patterning (stereotypy), as well as a scale of post-ictal suppression rating from 0-3, with “0” indicating no suppression, and a “3” indicating abrupt termination. While this post-
ictal suppression was useful for clinical purposes, more operationalized methods of scoring post-ictal suppression were needed. Additionally, this paper was the first to visually demonstrate a symmetry rating of 0, with much more intense ictal activity in the right channel than the left channel (Figure 6c). Post-ictal suppression was also demonstrated visually in two diagrams, one displaying a rating of 0.5 and the other, a rating of 2.5 (Figure 6e,f).

Figure 6: Visual ratings of symmetry and post-ictal suppression. Figure adapted with permission from: Nobler et al. (1993) EEG manifestations during ECT: effects of electrode placement and stimulus intensity. Biological psychiatry. 34(5):321-30.

Together, these texts have produced several measures of seizure ratings that have since been used in many studies for the qualitative analysis of EEG ictal recordings. These characteristics include: polyspike phase maximum amplitude and duration, slow wave phase maximum amplitude and duration, seizure symmetry, post-ictal suppression ratings (0-3), and global seizure strength ratings (0-6). Additional modification of the post-ictal suppression rating scale was created by McCall and
colleagues, with seizure ratings further operationalized into different categories with the following descriptions: 0= “cannot tell where seizure ends”, 1= “termination is clear but suppression is poor”, 2= “good suppression but gradual transition”, 3= “good suppression and abrupt termination” (McCall et al, 1996). These texts have since served as useful standardized measurements for the scientific community. Although additional operationalization for these measurements are useful, many research studies have used these original metrics to evaluate the relationship between seizure adequacy and therapeutic outcome.

**Using the inter-ictal EEG to Predict Treatment Outcome**

Since that time, other researchers have attempted to investigate whether these seizure characteristics are related to treatment efficacy in ECT. Minelli et al (2015) found that individuals with better quality seizures were more likely to respond to ECT treatment than those with poor quality rated seizures. Specifically, raters assigned one-point values for the presence of the following characteristics: EEG seizure length (>25 seconds), post-ictal suppression index (higher or equal to 80% suppression), wave amplitude (higher or equal to 180 microvolts), tachycardia (120 beats per minute) and hemispheric brain wave synchronicity. Based on these values, the seizures were rated as poor (score of 0-1.7), medium (score of 1.8-3.4) or good (score of 3.5-5). Those individuals with high and medium overall seizure ratings had significantly greater reductions in MADRS scores than individuals who had poor quality seizures (Minelli et al, 2015).

**Optimizing Parameters of Stimulation in MST**

While MST has shown promise as a potential alternative to ECT, little is known about the optimal stimulation parameters of treatment. In early clinical trials of MST, optimizing frequency of the pulse stimulus was limited by technological restrictions.
Standard repetitive transcranial magnetic stimulation (rTMS) devices allowed for 25 Hz stimulation, however, this proved difficult to induce intentional seizures in non-human primates (Lisanby et al, 2003b) and subsequent technological advancements allowing for 40 Hz stimulation were inconsistently able to induce seizures in human participants (Lisanby et al, 2003a). Current equipment allowed for higher stimulation frequencies without the risk of coil overheating. Frequency has been explored in ECT as a potential parameter to optimize therapeutic effectiveness while minimizing the electrical charge needed to induce a seizure (Girish et al, 2003; Roepke et al, 2011; Swartz and Manly, 2000), and has been shown to affect physiological characteristics of a seizure (Kotresh et al, 2004). For example, 25 Hz bilateral ECT was able to induce seizures at a lower stimulation threshold than 100 Hz stimulations (Girish et al, 2003). However, the effect of pulse frequency on the treatment seizure has yet to be explored in MST. Additionally, no published studies to date have investigated the effect of treatment frequency on therapeutic outcome and ictal seizure characteristics.

**Potential Mechanisms of Action**

The therapeutic mechanisms through which frontal MST exerts a clinical response are not clearly understood, and the characteristics of the induced seizures may inform our understanding of the biological mechanisms underlying its’ effectiveness. As such, the current study will attempt to elucidate biological changes occurring during MST stimulations at different frequencies. Using this information coupled with the results of previous studies can help shed light on the mechanisms behind its
effectiveness. Below we review our current theories in the field of convulsive brain stimulation to inform interpretations of the results of this study.
Chapter 2: Aims and Hypotheses

**Aim 1:** To characterize the ictal EEG from patients in an open label trial of MST using three different frequencies of stimulation (25, 50, and 100 Hz).

**Hypothesis 1:** We hypothesized that seizure characteristics may differ across seizures induced at different stimulation pulse frequencies.

**Aim 2:** To determine if there is a relationship between seizure measures and treatment outcome in MST, and whether our current understanding of seizure adequacy is an appropriate characteristic for magnetic seizure therapy.

**Hypothesis 2:** As in ECT, we hypothesized seizure characteristics can predict treatment response in patients undergoing MST. Moreover, we hypothesize the direction of these relationships will be the same as those seen in ECT.
Chapter 3: Materials and Methods

Patients

Patients with TRD were recruited from referrals to the Temerty Centre for Therapeutic Brain Intervention (TCTBI) at the Centre for Addiction and Mental Health (CAMH) in Ontario, Canada. An open-label parent study was registered on clinicaltrials.gov and received approval from the Research Ethics Board at CAMH, as well as Health Canada. Patients signed informed consent for clinical, cognitive, and seizure data collection, and biological information such as EMG, EEG, heart-rate, and blood pressure are routinely recorded for all patients receiving MST treatment. Patients were enrolled in treatment with three different frequencies in a non-randomized open-label trial, with enrollments for one frequency group occurring at any given time. The first set of participants were exposed to 100 Hz MST, which is the most common frequency used to date in studies using the new MagPro MagVenture. This study was designed to identify the optimal treatment frequency for a novel coil placement prior to conducting a randomized controlled trial. As such, pilot data was collected and sampling was continued when enough clinical data had been collected. 50 Hz was subsequently administered and 25 Hz followed. While the open-label trial sought to investigate the effects of MST on schizophrenia, unipolar and bipolar depressed patients, and OCD patients. The sample size for other diagnoses collected were too small to draw any meaningful conclusions, and previous research has shown seizure characteristics (Nobler et al, 2000) and response rates in ECT (Daly et al, 2001) differ between those diagnosed with bipolar and unipolar depression. It was important to maintain a circumscribed sample for result interpretation and as such, for the purpose of this analysis, only patients with unipolar depression were analyzed.
Patients were eligible for MST treatment if they had a diagnosis of a current MDD episode with or without psychotic features based on the DSM-IV-TR SCID criteria, were between the ages of 18-85 at the time of study enrolment, had a 24-item Hamilton Depression Rating Scale (HAMD-24) score of > 21, were capable to consent to the treatment, and were on an acceptable form of birth control if they were a woman of child bearing age. Patients were not eligible for MST treatment if they had an unstable medical and/or neurological condition, were pregnant or lactating at the time of study, were deemed unfit for anesthesia, had a cardiac pacemaker, cochlear implant, implanted electronic device or ferrous metallic implant in the cranium, were on a benzodiazepine at a dose greater than 2 mg lorazepam or equivalent, were taking any non-benzodiazepine anticonvulsant, had active substance abuse or dependence within the last 3 months prior to treatment initiation, had a diagnosis of delirium, dementia, or another cognitive disorder secondary to general medical condition at the time of study, had a lifetime diagnosis of an eating disorder, or had a history of suicide attempts in the 6 months prior to treatment. For a complete list of patient demographics refer to Table 1
Figure 7. Patient Selection

Provided Consent: n=160

- Withdrew Consent (n=1)
- Did not pass screening criteria (n=33)

100 Hz
- OCD (n=2)
- SCZ (n=2)
- BPD (n=10)
- MDD Assessed for eligibility (n=28)
  - Ketamine/Labetalol (n=1)
  - Contaminated or uncollected EEGs (n=16)
  - Final Sample (n=11)
  - Seizures (n=37)

50 Hz
- OCD (n=1)
- SCZ (n=2)
- BPD (n=3)
- MDD Assessed for eligibility (n=22)
  - Contaminated or uncollected EEGs (n=5)
  - Final Sample (n=16)
  - Seizures (n=62)

25 Hz
- OCD (n=3)
- SCZ (n=3)
- BPD (n=6)
- MDD Assessed for eligibility (n=46)
  - Contaminated or uncollected EEGs (n=11)
  - Final Sample (n=34)
  - Seizures (n=137)
Table 1.

Demographic data

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<th></th>
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<td>Female (n)</td>
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<td>Age (in years)</td>
<td>53</td>
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<tr>
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<td>724.19</td>
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Number of Treatment sessions analyzed with the following medications

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<td></td>
<td></td>
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<tr>
<td>Remifentanil</td>
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Medications at Baseline (n)

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Average Doses

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Anesthesia

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<tr>
<td>Glycopyrrlate</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>Kytril</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Granisetron</td>
<td>0.00</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>0.00</td>
<td>0.50</td>
<td>0.00</td>
</tr>
<tr>
<td>Methohexital after seizure</td>
<td>0.108</td>
<td>0.032</td>
<td>0.121</td>
</tr>
</tbody>
</table>
Anesthesia and Treatment

Patients received either a) methohexital sodium (approximately 0.75mg/kg) or b) a combination of methohexital sodium (approximately 0.375 - 0.5mg/kg) and remifentanil hydrochloride (approximately 1.0 - 1.5 mcg /kg) for anesthesia. Once patients were non-responsive, muscle relaxant, succinylcholine chloride was used (approximately 0.5mg/kg) to attenuate robust physical convulsions. Other non-psychotropic medication may have been given for different medical conditions. All medications administered in the treatment room are listed in Table 1 and differences in dosing across groups are presented. Previous research has shown medications given in treatment, such as propofol and methohexital, can significantly affect seizure characteristics (Akcaboy et al, 2005). To ensure all significant variance in the data due to drug administration was accounted for, we conducted preliminary analyses of all medications and their relationship to seizure characteristics, controlling for age, gender, frequency and number of stimulations. These analyses demonstrated absolute dose of methohexital, remifentanil, and succinylcholine did effect several seizure characteristics at p<.2, and thus, doses were used as covariates for all hypothesis testing.

Seizures following the administration of labetolol were excluded from analyses due to its anticonvulsant properties. Similarly, seizures where ketamine was used as the induction were not included as it has no anticonvulsant properties and comparison with seizures where methohexital was used for induction could be problematic. Respiration rate and heart rate were monitored throughout treatment, and diastolic and systolic blood pressure measures were collected before and after each treatment session. If inadequate dosing of anesthesia was provided, post-midazolam was given to reduce the phenomenon of emergence paralysis upon wakening.
MST Titration and Treatment Course

Prior to anesthesia, patients were fitted to the MST twin coil using tape with reference points placed on the forehead to ensure consistent coil placement at every treatment. Twin coil spacing between electrodes were adjusted to ensure a close fit and account for anatomical differences. Patients were given ear plugs to protect their hearing from the potential adverse effects of the stimulation pulse trains. MST stimulation at a frequency of 25, 50 or 100 Hz was delivered over the frontal cortex using a twin coil (MagPro MST; MagVenture) and MST stimulator (Magventure A/S, Farum, Denmark). Once patients were anesthetized, physicians monitored the cessation of voluntary movement. The twin coil was placed with the arrows pointing anterior-posterior indicating the initial direction of the biphasic current, with the center of each coil positioned over F3 and F4 in accordance with the 10-20 system, with the coil e-fields meeting at approximately a 90-110 degree angle in order to achieve the greatest depth-to-spread ratio (Deng et al, 2015). This location was chosen as it results in a maximal field strength summation at the midline frontal and prefrontal cortices corresponding to the Fz electrode site of the 10-20 system (Sun et al, 2016). As mentioned, the prefrontal cortex is thought to regulate emotion, reward and cognition, and induced neuroplastic changes may help improve symptoms of depression.

At the end of the stimulus train, the coil was removed from the forehead and EEG recording electrodes were placed approximately one-inch above the left and right eyebrow. EEG recordings continued until seizure termination was clear or, in rare instances, when reorientation was clear indicated by the onset of spontaneous respiration. Patients were ventilated throughout treatment and efforts were made to minimize interference with the EEG leads and electrodes. In the event of a
prolonged seizure, seizures were terminated with the administration of anticonvulsant medication to negate the risk of entering status epilepticus. All patients underwent a dose titration procedure to establish their convulsive stimulation threshold with machine intensity set at 100% stimulator output. If a seizure was not induced with the first stimulation, increasingly longer train durations were administered at least 30 seconds after the previous stimulation, starting with 2 seconds in the 100 and 50 Hz group, and 4 seconds in the 25 Hz group, and increasing by 2 seconds and 4 seconds respectively with each additional stimulation. For all subsequent treatments, the stimulation was 4 seconds longer in the 100 and 50 Hz group and 8 seconds longer in the 25 Hz group than the seizure threshold stimulation duration, to a maximum of 10 seconds and 20 seconds respectively. A maximum of 1000 pulses was delivered to a patient for any given treatment stimulation.

Treatment course durations varied on a case by case basis. Treatment occurred at a rate of 2-3 sessions per week, with the 24 treatments being the maximum number administered in an acute course. Patients could be discontinued from treatment by an overseeing psychiatrist if there was no perceived benefit to treatment, and patients could withdrawal from the study at any time for any reason. As this was a treatment study, all individuals who withdrew from the study did so due to an inability to tolerate treatment side effects, lack of perceived benefit or worsening symptoms, or for personal reasons Additionally, patients completed a treatment course once they met remission criteria two weeks in a row following MST treatment. The earliest time point for remission occurred in 6 treatments.
Right and left fronto-mastoid ictal EEG recordings were collected using pediatric EKG pads during each treatment (Figure 8). As the coil partially rests over the forehead during stimulation, the EEG electrodes were placed on the forehead immediately following stimulation. Reference electrodes were placed on the mastoids of each respective hemisphere, and the ground electrode was placed on the clavicle. Paper traces of ictal recordings were collected in real-time using the MECTA Spectrum 5000Q EEG monitor, with the gain maintained at a low-medium setting (0.5 mv/mm).

Seizure Ratings

Ictal EEG recordings were assessed based on the following characteristics: polyspike phase maximum amplitude (μV) and duration (s), slow-wave phase maximum amplitude (μV) and duration (s), post-ictal suppression rating (0-3), symmetry rating (0-3) and global seizure strength (0-6). The ratings were conducted
in accordance with previously published methods (Azuma et al, 2007) (Bewernick et al, 2010) (Coffey, 1993) (McCall et al, 1996) (Nobler et al, 1993). Two modifications to the rating scales were used and are illustrated in Figure 9 and 10.

Figure 9: this image displays a modified post-ictal suppression rating scale of the written descriptions developed by McCall et al. (1996)
Figure 10. This figure displays a modified scale for rating symmetry between both hemispheres.

To maintain consistency, a visual representation for rating post-ictal suppression was used in conjunction with the previously published rating scale (Figure 6). A symmetry rating scale was developed, with a score of 3 indicating the highest degree of symmetry, while a 0 indicates much stronger activation in one hemisphere over the other (Figure 8). Additionally, a composite metric of overall seizure adequacy was given to each seizure. Seizures received one point for meeting each of the following criteria: 1) a maximum EEG seizure amplitude ≥\(750\) μV, 2) a motor duration ≥15 seconds, 3) a total EEG duration ≥25 seconds, 4) a symmetry score ≥2 5) a post-ictal suppression score ≥2, and 6) a global seizure strength rating ≥4. The seizure composite metric was therefore scored on a scale of 0-6.

Inter-rater reliability of the scoring method was confirmed between the two raters (F.A.B. and Y.N.) prior to data analysis. Treatments 1, 6, 12, 18 and 24 were the
primary targets of analysis; however, if the EEG data for those specific treatment sessions was contaminated with artifact, the prior or subsequent treatment session EEG recording was used. Up to 5 treatment sessions were analyzed from each participant, with less seizures analyzed if patients did not undergo the maximum number of treatments. The primary rater scored the seizure data (F.B.), and when ambiguities in the data arose (less than 2% of all seizures analyzed), a second rater’s input (Y.N.) was also used to assess or remove the data from analysis. Raters were blind to treatment outcome, treatment session, and treatment frequencies of all ictal recordings. All individuals who met criteria for inclusion in this study were included in the present analysis. As such, the integrity of the blind was well-maintained.

Clinical Outcome Measures

Trained research analysts conducted all clinical and cognitive assessments. The primary outcome measure used was the 24-item HAMD (Hamilton, 1960). A full clinical and cognitive battery incorporating this measure was conducted up to two weeks before and after the course of treatment, as well as on every 6th treatment. Clinical assessments included the HAMD, Quick Inventory of Depressive Symptoms (QIDS), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and Beck’s Scale for Suicidal Ideation (SSI) to monitor patient response. Cognitive assessment measures included the Montreal Cognitive Assessment (MoCA), the Matrix battery, including Repeated Battery for Neuropsychological Status (RBANS), Trails-Making Test B, and the Autobiographical Memory Interview (AMI) was completed pre- and post- treatment. Due to the lack of variability in the SSI measure, relationships between suicidal symptom severity and seizure characteristics could not be analyzed, and due to the lack of reported cognitive side effects in MST, relationships between seizure characteristics and cognitive side
effects would not be clinically meaningful and would warrant very high sample sizes to reveal any relationships. As such, this study remained focused on the relationship between seizure characteristics and treatment outcome across different frequency groups.

**Analysis**

Preliminary exploratory analyses were conducted to determine which covariates had a significant impact on the dependent variables. Any variables with a $p < .2$ were included in the analyses to ensure all potential covariates were accounted for. Regardless of significance, gender, age, methohexital dose were included in the analyses as their effect on seizure adequacy measures has been established in the literature.

Mixed effects models were used to evaluate differences between groups to account for within-subject correlation for data with continuous dependent variables. For ordinal data, (the effect of treatment frequency on symmetry and post-ictal suppression) ordinal logistic general estimating equations were used. For dependent data with positively skewed residuals (polyspike amplitude), gamma link general estimating equations were used instead. All analyses comparing frequency groups controlled for gender, age, total number of stimulation pulses, baseline medications, doses of methohexital, succinylcholine and remifentanil, and whether the individual received sodium citrate at the time of treatment. The direct effect of number of pulses was also evaluated to determine whether it predicted treatment outcome independent from treatment frequency and was assessed using the following controls: frequency, gender, age, baseline medications, doses of methohexital, succinylcholine and remifentanil, and whether the individual received sodium citrate at the time of treatment. The effect of seizure characteristics on treatment outcome as measured by the HAMD was evaluated using a series of mixed effect models when the residuals were normal. As the dependent variables met the assumption of
normality, no other tests were used. Corresponding Wald chi-square and F-values were reported in Table 2 and 3 for all tests of significance. The reported means for significant differences in frequency have been adjusted for covariates. Both the raw and adjusted means are reported in Table 2.
## Table 2.
Seizure Characteristics Across Treatment Frequencies

<table>
<thead>
<tr>
<th>Seizure Characteristics</th>
<th>Adjusted</th>
<th>Unadjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 Hz</td>
<td>50 Hz</td>
</tr>
<tr>
<td></td>
<td>F/X^2</td>
<td>F/X^2</td>
</tr>
<tr>
<td>Max. Polyspike Amplitude (µV)</td>
<td>311.0 (23.05)</td>
<td>334.6 (29.0)</td>
</tr>
<tr>
<td>Polyspike Duration (seconds)</td>
<td>4.01 (0.85)</td>
<td>3.39 (1.00)</td>
</tr>
<tr>
<td>Max. Slow-wave Amplitude (µV)</td>
<td>573.65 (23.25)</td>
<td>596.33 (27.2)</td>
</tr>
<tr>
<td>Slow-wave Duration (seconds)</td>
<td>29.44 (3.37)</td>
<td>47.51 (3.94)</td>
</tr>
<tr>
<td>Post-ictal Suppression (0-3)</td>
<td>1.62(0.02)</td>
<td>1.70 (0.12)</td>
</tr>
<tr>
<td>Global Seizure Strength (0-6)</td>
<td>4.40 (0.16)</td>
<td>4.29 (0.19)</td>
</tr>
<tr>
<td>Symmetry (0-3)</td>
<td>2.03 (0.09)</td>
<td>2.00 (0.10)</td>
</tr>
<tr>
<td>Motor Seizure Duration (seconds)</td>
<td>29.80 (2.2)</td>
<td>41.57 (2.65)</td>
</tr>
<tr>
<td>EEG Seizure Duration (seconds)</td>
<td>43.75 (3.36)</td>
<td>60.23 (4.01)</td>
</tr>
</tbody>
</table>
Chapter 4: Results

Effect of Frequency on Seizure Characteristics

Slow-wave duration differed significantly between the frequency groups, both when adjusted \( F(2,212) = 6.254 \) \( p = .002 \) and not adjusted for covariates \( F(2,151) = 8.543, p < .001 \), with 100 Hz mean(SE)=22.667(4.235) having significantly shorter slow-wave durations than the other two groups, and the 25 Hz group mean(SE)=29.440(2.491) also having significantly shorter slow-wave durations than the 50 Hz group mean(SE)=47.509(5.332) (Figure 10). Global seizure strength was shorter in the 100 Hz group mean(SE)=3.292 (.290) than the 25 Hz group mean(SE)=4.395 (.163) and 50 Hz group mean(SE)=4.293 (.187), both when adjusted for covariates \( F(2,155) = 5.735, p = .004 \) and when unadjusted \( F(2,217) = 5.456, p = .005 \) (Figure 11). Motor duration was longest in the 50 Hz group mean(SE)=41.574(3.633) compared to the other two groups, and 25 Hz mean(SE)=29.793(1.737) motor seizure duration was significantly longer than the 100 Hz group mean(SE)=24.231(1.898). These group comparisons were significant when the covariates were included in the analyses \( F(2,171) = 8.613, p < .001 \) (Figure 12) and without adjusting for covariates \( F(2,242) = 5.335, p = .005 \). Total EEG duration differed among the three treatment groups, and the 50 Hz mean(SE)=60.230, (5.145) had longer durations than the other two groups 25 Hz mean(SE)=43.747(2.743) 100 Hz mean(SE)=40.154(4.696) \( F(2,171) = 6.190, p = .003 \) (Figure 13), and was significant without accounting for covariates \( F(2,241) = 3.516, p = .031 \). Finally, the composite metric used to evaluate total seizure adequacy differed among the three groups, with 25 Hz mean(SE)=3.446(0.145) and 50 Hz mean(SE)=3.445(.147) having better seizures than the 100 Hz group mean(SE)=2.208(.217) \( F(2,153) = 10.585, p < .001 \) (Figure 14), and was a robust
unadjusted finding $F(2,214)=13.906, p<.001$. All other variables did non-significantly differ among treatment groups and are displayed in Table 2.

Mixed effect models revealed number of pulses significantly negatively affected polyspike amplitude $X^2(1,7)=26.315, p<.001$, polyspike duration $F(1,147)=23.250, p<.001$, slow-wave duration $F(1,152)=13.113, p<.001$, motor seizure duration $F(1,172)=17.798, p<.001$ and the EEG duration $F(1,172)=19.289, p<.001$. Higher number of pulses caused shortened polyspike and slow-wave phase durations, total EEG durations, and shortened motor duration.

**Seizure Characteristics and Treatment Outcome**

Change in HAMD score from baseline to the end of treatment was significantly impacted by polyspike duration $F(1,146)=5.812, p=.017$ and slow-wave amplitude $F(1,150)=3.986, p=.046$, with greater reductions in HAMD having shorter polyspike durations and smaller slow-wave amplitudes. All other statistical outcomes are non-significant and displayed in Table 3.
Figure 11: Slow-Wave Duration Differences Across Frequencies

Figure 12: Global Seizure Strength Differences Across Frequencies
Figure 13: Motor Duration Differences Across Frequencies

Figure 14: EEG Duration Differences Across Frequencies
Figure 15: Seizure Adequacy Differences Across Frequencies
Table 3. Relationship Between Seizure Characteristics and Clinical Outcome/ Number of Pulses

<table>
<thead>
<tr>
<th>Mixed Models</th>
<th>Change in HAMD</th>
<th>Number of Pulses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>coefficient</td>
</tr>
<tr>
<td>Seizure Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyspike Amplitude (µV)</td>
<td>6.68</td>
<td>-0.036</td>
</tr>
<tr>
<td>Polyspike Duration (seconds)</td>
<td>6.74</td>
<td>-0.221</td>
</tr>
<tr>
<td>Slow-wave Amplitude (µV)</td>
<td>7.32</td>
<td>-0.037</td>
</tr>
<tr>
<td>Slow-wave Duration (seconds)</td>
<td>7.34</td>
<td>-0.012</td>
</tr>
<tr>
<td>Post-Ictal Suppression (0-3)</td>
<td>7.52</td>
<td>-0.232</td>
</tr>
<tr>
<td>Global Seizure Strength (0-6)</td>
<td>7.37</td>
<td>-0.732</td>
</tr>
<tr>
<td>Symmetry (0-3)</td>
<td>7.48</td>
<td>0.9926</td>
</tr>
<tr>
<td>Motor Seizure Duration (seconds)</td>
<td>7.69</td>
<td>-0.037</td>
</tr>
<tr>
<td>EEG Seizure Duration (seconds)</td>
<td>8.72</td>
<td>-0.022</td>
</tr>
<tr>
<td>Total Composite Metric (0-6)</td>
<td>82.70</td>
<td>-0.464</td>
</tr>
<tr>
<td>Number of Pulses</td>
<td>7.69</td>
<td>0.004</td>
</tr>
</tbody>
</table>


Chapter 5: Discussion

Frequency: Comparison to ECT

The results of this study indicate that MST stimulation frequency did influence several seizure characteristics, namely, the EEG duration of the slow-wave phase, global seizure strength, motor duration, total EEG duration, and overall seizure adequacy.

The 100 Hz group tended to have worse seizure characteristics than the other two groups, as defined by current ECT quality standards, while 50 Hz tended to have the best seizure characteristics. A previous ECT study has shown that 30 and 60 Hz ECT did not differ with respect to seizure threshold, but pulse-widths of 1 ms were less efficient at seizure induction than 0.5 ms stimulations (Kotresh et al., 2004; Swartz et al., 2000). This study did not incorporate seizure characteristic measures, and used a counterbalanced within-subject design. As such, treatment outcome could not be evaluated. To our knowledge, no ECT studies to date have incorporated as many frequency comparisons as the present study, so extrapolations from ECT literature is limited.

Using a wider range of stimulation frequencies, traditional one-millisecond brief-pulse ECT demonstrated 25 Hz was superior to 100 Hz ECT at inducing seizures at lower thresholds (Kotresh et al., 2004(K. Girish, 2003). In accordance with these papers, further research indicated 40 Hz RUL ECT was significantly better at reducing depressive symptoms after 9 treatment sessions than 100 Hz ECT, using bidirectional ultra-brief pulses and charge-matched stimulations (Roepke et al., 2011). In ECT research, lower frequencies tend to induce seizures at lower
thresholds than higher stimulation frequencies. While we noted differences consistent with this phenomenon between 100 and 25 Hz seizure characteristics, 50 Hz unexpectedly induced better seizure characteristics than the 25 Hz group in all of the motor and EEG duration categories. For further interpretation of these results, we will review them in the context of neuronal processes.

Possible Mechanisms Behind Frequency Differences

Stimulus Crowding

One hypothesis for the differences in seizure adequacy measures across frequencies involves neuronal firing properties. Before a second action potential can be fired, the neuron must recover from the first action potential. This refractory period may be too short in the 100 Hz group for the neuron to fully recover, and as such, the stimulation frequency may not be optimal to induce robust long lasting seizures, an effect known as ‘stimulus crowding’ (Peterchev et al, 2010). Other research has shown extracellular repetitive high-frequency (100-250 Hz) electrical stimulation to subthalamic nucleus neurons for one minute causes blockade of ionotropic channels, including Ca++ and Na+ channels, delaying increases to the membrane potential, and thus decreasing the probability of firing subsequent action potentials. This research supports the hypothesis that high-frequency stimulation is sub-optimal for suprathreshold stimulation (Beurrier et al, 2001). While the stimulus trains were set to a maximum of 1000 pulses in the present study, the 100 Hz group had the shortest seizure durations relative to the other two treatment groups, which may suggest similar biological mechanisms occur at shorter train durations. However, the Beurrier et al. 2001 study did not analyze frequencies below 100 Hz,
and as such, the effects of lower frequencies on cation channel blockade are difficult to interpret.

Based on the results of the current study, one may predict 25 and 50 Hz stimulations were not fast enough to induce this ion-channel blockade, and thus, do not impair the regular spike and wave patterns as in ECT.

**Stimulation Frequency and Cellular Hyperpolarization**

Measuring the effects of extracellular stimulation on cellular activity in the human brain is not without challenges. One way to mitigate this problem is to perform simulation analyses using information we have gathered from cellular research. A simulation study evaluating the effect of extracellular electrical stimulation to the dendrites at different frequencies and amplitudes can provide insights into the differences in seizure characteristics we see across stimulation frequencies. It was observed that initial inhibitory post-synaptic potentials (IPSPs) cause different hyperpolarization effects on the soma depending on the rate of stimulation at the cellular dendrites, with longer periods of hyperpolarization occurring prior to stimulus trains at higher frequencies (Hernandez et al, 2015).

**Normal Neuronal Firing Patterns**

A simulation study demonstrated that interneuron 40 Hz oscillations of inhibitory postsynaptic potentials (IPSPs) entrained pyramidal cells, which initially oscillated between 32-47 Hz, to fire synchronously coupled with interneuron cell firing (Lytton and Sejnowski, 1991). Pyramidal cells oscillating below 32 Hz at baseline can partially be entrained in a less robust manner, however above 47 Hz this entrainment fails. This suggests stimulations should be near typical neuronal firing rates to induce phase-locking and frequency entrainment, as in the slow-wave
phase of the seizure. The 25 Hz stimulation was significantly better at inducing longer motor durations and slow-wave durations than the 100 Hz, but was also less effective than the 50 Hz frequency. Our results, with the aforementioned study, suggest the 50 Hz stimulation better matches the firing rates of the target brain regions.

**Frequency and Changes to Chemical Messenger Systems**

Previous research has shown high-frequency stimulation (>100 Hz) to the subthalamic nucleus (STN) decreased serotonergic firing of the dorsal raphe nucleus (DRN) (a major serotonergic projection site to the frontal cortex), while stimulations at or below 50 Hz did not change serotonergic firing in the DRN. It is possible stimulation of these pathways from the opposite direction stimulating the (frontal cortex) induces similar effects. As such, serotonergic stimulation may not be as efficient in 100 Hz stimulations compared to the other two groups.

The DRN provides major serotonergic projections to the prefrontal cortex, and as such, frontal MST may be exerting indirect effects on the PFC-DRN projections pathways. This theory is supported by research in electroconvulsive therapy, which shows ECT induces neuroplastic changes in serotonergic firing (Yatham et al, 2010) and thus frontal MST may be inducing similar changes. Studies in rodents have shown high frequency (0.2 Hz-15 Hz) medial prefrontal stimulation with long train durations (5 minutes) increases serotonin clearance time in DRN and decrease neuronal firing of the DRN (Srejic et al, 2016). Stimulation of the mPFC induces inhibition and excitation during the slow-wave phase of the seizure and has been related to GABAergic and serotonergic release in the DRN. Stimulating projection neurons in the mPFC excites GABAergic neurons, which in turn inhibits serotonergic and glutamatergic processes in the DRN during the seizure. While the frequency
parameters explored in this study were much higher than those in the rodent studies, this research was conducted on humans and neural firing rates have been shown to vary across species (Mochizuki et al, 2016). As such, it is difficult to extrapolate this information from rodents to the human population, and further research involving PET imaging is necessary to understand the therapeutic mechanisms of action in MST.

Limitations of Frequency Comparisons

Indeed, while the differences in seizure characteristics across frequency groups may be the result of the true effects of stimulation frequency, due to the intensity roll-off of the coil output, 100 Hz stimulations were performed at an amplitude of approximately 70% of stimulations applied in the other two groups, and as such, the effect of stimulation intensity is a confounding variable. Interestingly, the results of this study could suggest lower, not higher, intensities result in better treatment outcome. The primary focus of MST device developments to date have been to increase the current amplitude inside the coil. Given that shorter polyspike duration and lower slow-wave amplitude were related to better treatment outcome, and 100 Hz had significantly poorer related metrics (global seizure strength and EEG durations), these results may support the hypothesis that higher intensity is not necessarily therapeutically superior.

In fact, clinical results of an overlapping treatment sample revealed a relationship between baseline measures of inhibition and remission of suicidal ideation, suggesting ictal metrics involved in inhibition may provide insight into remission of suicidal ideation as well. Unfortunately, the statistics required of this dataset did not permit the analyses of SSI, but outcome differences in the present frequency samples demonstrated no significant differences in reduction of depressive symptoms, but greater reductions of suicidal ideation in patients treated with 100 Hz
compared to the 25 and 50 Hz treated samples. Indeed, it is difficult to parse out the effects of stimulation intensity and frequency from this study, as comparisons would require a) the development of new devices with limited coil current amplitude roll-off or b) reduced stimulation output at lower frequencies. While the latter is a possibility with current MST devices, it is an unlikely exploratory investigation, as most developments have focused on increasing the magnetic field strength generated by MST. Performing a proof-of-concept study such as this one would ease the identification of the effects due to intensity opposed to frequency.

One of the earliest investigators of MST, Dr. Sarah H. Lisanby, along with colleague and electrical-field analyst Dr. Zhi De Deng, contributed a chapter on MST to a diverse book describing evolutions of brain stimulation interventions (Reti, 2015). In this chapter, they explained several useful concepts of MST that have not necessarily been explicitly published in peer reviewed literature (Lisanby and Deng, 2015).

An interesting point the authors made was that first attempts to create high-dose MST by switching from 50 Hz to 100 Hz did not work as expected. In fact, these authors report 10-25 Hz was the optimal frequency to induce seizures. This paper was published in 2015, after the twin-coil and MagPro MagVenture devices were available for research testing. However, it is unclear whether the 3rd or 4th generation device was used to draw this conclusion, and as such, it is important to note extrapolating this information to the present study should be made with caution.

**Stimulation Pulses**

The study noted a negative relationship between the number of stimulation pulses and seizure characteristics despite controlling for frequency. It is important to note the direction of this relationship remains unclear.
The idea that a smaller number of stimulation pulses in a train is optimal for treatment efficacy is one possibility. Continuous stimulation pulses induce a cumulative effect of depolarized neurons with each pulse, and eventually leads to a seizure. However, like frequency, there may be a limit to the most effective number of pulses that may be exceeded in MST. As demonstrated by simulation studies (Deng et al, 2011), the total e-field of MST is confined to localized superficial cortex. It may be that we are overstimulating the total brain volume included in the e-field with a maximum of 1000 pulses, despite being half the maximum number of pulses permitted for ECT use. Future research using fewer pulses is warranted to further optimize treatment.

The authors used number of pulses as a measure of seizure threshold and maintained that more pulses were required to induce a seizure at higher frequencies. Our study falls in line with this observation in that the 100 Hz group received more pulses per session on average than the 25 and 50 Hz. However, it is possible the train duration may be responsible for these effects specifically in the 25 Hz. Perhaps stimulating brain tissue requires a certain number of seconds to induce a seizure opposed to number of pulses. In this case, matched train durations would cause a two- and four-fold difference compared to the 25 Hz stimulations, in the number of pulses delivered in the 50 and 100 Hz groups respectively.

An important finding from this study is that number of stimulation pulses had a greater effect on seizure characteristics than frequency. Continuous stimulation pulses induce a cumulative effect of depolarized neurons with each pulse, and eventually leads to a seizure. Stimuli that are matched in electrical charge are more efficient at inducing a seizure when they have a higher number of pulses (Peterchev et al, 2010). The reader is cautioned to be conservative when interpreting these results as it is likely it may be due to confounding effect of increased seizure
threshold. To review, those with higher seizure thresholds require a larger number of pulses as well as having lower quality seizure characteristics. Moreover, a higher number of pulses correlated with a lower treatment response, also likely due to the need for increased dose when patients are not responding well to treatment. Previous research in ECT has demonstrated a link between increased seizure threshold across treatment and better clinical response. However, this study did not demonstrate any significant changes in EEG characteristics across treatment courses, suggesting the mechanisms of action responsible for the effectiveness of MST may differ from those of ECT.

An alternative explanation may better explain the relationship between number of pulses and treatment outcome. The maximum number of pulses in a stimulation session was fixed at 1000 pulses with the MagVenture MagPro device, and the 50 and 100 Hz stimulations were matched for maximum number of pulses delivered (1000 pulses). However, the 25 Hz group received a maximum of 500 pulses for stimulations up to 20 seconds in length, and as such, additions to the length of the stimulus may provide further insights into the importance of treatment frequency. Unfortunately, the data collected in this sample did not have an unlimited number of pulses, and as such, results cannot be deemed causational. There was a trend for higher number of pulses delivered to have weaker seizure characteristics, but individuals with poor seizures were identified as having high seizure thresholds, and as such, the dose was increased at a faster rate. It is likely the relationship between number of pulses and seizure outcome metrics is not a direct causal relationship. Further research utilizing devices capable of administering longer train durations at high frequencies would help to interpret the direction of these results.
EEG Predictors of MST Treatment Outcome

Shorter polyspike duration was significantly related to reduced depressive symptoms, supporting previous findings from ECT demonstrating a relationship between short latency to the slow-wave phase and treatment outcome (Krystal et al, 1995). One hypothesis to account for this finding is that 20% of the IPSPs of inhibitory interneurons are required to be synchronized in order for entrainment of synchronous pyramidal cells to fire intermittently (as it does in the slow-wave phase) (Lytton et al, 1991). It is possible that those seizures expressing short latency to the slow-wave phase are achieving entrainment more quickly, which is a potential therapeutic mechanism of action.

Of note, the present study did not find a significant relationship between post-ictal suppression and treatment outcome. This is an unexpected finding compared to previous studies evaluating treatment efficacy in ECT, and may demonstrate less involvement of GABAergic neuronal firing than in ECT. These results do support previous findings in MST suggesting post-ictal suppression is less robust and less clearly seen than in ECT, suggesting the lack of significance is not a type II error (Kayser et al, 2015; Lisanby et al, 2003a). Regarding possible mechanisms to account for this difference, a pure layer of GABAergic neurons exists in the thalamic reticular nucleus, and in generalized seizures these neurons are excited as thalamocortical projections are stimulated (Blumenfeld, 2005). GABAergic signals are sent back to the thalamus via feedback loops, and seizure activity is suppressed (Blumenfeld, 2005). As MST induces a more focal electrical stimulation, it may not reach the thalamic nuclei, and thus may not induce the GABAergic processes necessary for total seizure suppression. This is not to say no inhibition exists, but the lack of immediate and sharp suppression of ictal activity in MST
suggests inhibitory mechanisms are not as potent in MST as in ECT, and thus MST may exert its therapeutic effects through the mediation of different biological pathophysiological abnormalities in depression. Additionally, no change in ictal expression was seen across the treatment course, suggesting seizure threshold may not be related to treatment outcome and/or have an impact of ictal recordings in MST.

Perhaps counterintuitively, this study showed smaller slow-wave amplitudes were related to better treatment outcome on the HAMD. This contradicts research in ECT, where higher slow-wave amplitude is associated with better treatment outcome (Minelli et al, 2015). The reasons for these differences are not immediately apparent, yet other reports have noted significant reductions in MST ictal EEG amplitude compared to typical ECT seizures (Fitzgerald et al, 2013; Kayser et al, 2015). As immediate post-ictal suppression is not imminently clear in most MST stimulations, we hypothesize this result may be the combination of the onset of inhibitory processes overlapping excitatory ictal activity near the site of stimulation. In ECT, the robustness of a seizure coupled with its immediate termination is indicative of a high-quality therapeutic seizure, and is believed to be the result of continued seizure activity in almost all areas of the cortex, followed by synchronized inhibition. However, the immediate area stimulated by MST is far less than that of ECT (Deng et al, 2011), and as such, seizure induction in the targeted brain area happens quickly, and may take less time for inhibitory processes to begin. Clinical observations support this hypothesis, in that motor seizure induction begins during the MST stimulation, while in ECT, the motor seizure occurs after the stimulation. MST motor and EEG seizures are shorter, less robust, and usually a lack obvious post-ictal suppression (Fitzgerald et al, 2013; Kayser et al, 2013).
It is important to note other research evaluating seizure characteristics between responders and non-responders of MST failed to find ictal-EEG predictors of treatment outcome (Kayser et al, 2015). Other work has noted no obvious EEG pattern related to treatment response (Fitzgerald et al, 2013). While predictive outcome measures were not found, these studies were both limited by very small sample sizes which would likely not be able to statistically identify established predictors of ECT response. Additionally, both studies applied MST stimulations to the vertex while recording distally at the prefrontal cortex. It is well known that signal depletion from activity in a distal location occurs at distal electrodes. As such, further sites of stimulation result in lower amplitude at prefrontal recordings where EEG activity is dampened, and thus, its evaluation is less informative. However, the quality of the EEG signal dissipates the further away the recording site is from the site of stimulation, suggesting the lack of differences may not be seen in stimulations performed at the site of recording. Future vertex MST using EEGs at the site of stimulation may help to support the relationship between ictal-EEG characteristics and treatment outcome.

**Study Limitations**

A limitation to be acknowledged in interpreting the findings of this study is our method of recording and its impact on polyspike information. As we were recording EEG close to the site of stimulation, the first part of the seizure recordings was approximately 3 seconds after the stimulation. As the motor seizure begins during the MST stimulation, our recordings may have entirely missed the polyspike phase. In the event where no polyspike activity was present on the recording, we considered the polyspike amplitude missed information, and the polyspike duration, a zero. This may have contributed to more robust differences in the data, as all
polyspike durations shorter than 3 seconds were considered absent. Recording at a different location other than bi-frontally may mitigate this issue; however, amplitude and global seizure strength information would not have been as robust. We consider this limitation an appropriate cost to the benefit of recording at the site of stimulation.

Another limitation relates to the differential effect of number of treatments received as further treatments were contingent on symptom improvement and those that were not improving may have dropped out early. As such, survival curve analyses could not be performed to determine which time point seizures could be used to predict treatment outcome as drop-outs did not occur at random. However, averaging the seizures across treatments for each participant yielded very similar results to including 244 individual data points in the analysis, suggesting variance between treatment sessions does not impact the seizure characteristics enough to be clinically relevant.

Due to the open-label, non-randomized nature of the clinical trial, the treatment frequency groups varied greatly in their sample sizes. Although the participant sample sizes were uneven, up to 5 seizures were analyzed per patient, reducing within-subject variability. Also, the reduced sample size increases the risk of a type II error opposed to a type I error, and as such, we are confident the significant results were true effects.

The 25 Hz sample size was quite large relative to the other two groups because initial clinical data varied greatly from the latter portion collected, and as such, an increased sample size was needed to better understand the average clinical response to this treatment group. EEG data collection for the current study began half-way through the 100 Hz treatment period, and as such, the group has a smaller sample size. However, we analyzed up to 5 recordings per participant, and our total data sample included 244 EEGs in the analysis.
Moreover, due to the lack of significant impairments in learning and memory after MST, predicting cognitive outcome using MST ictal seizures was not a clinically meaningful exploration. While, ECT studies have demonstrated a link between seizure characteristics and cognitive side effects, it was later revealed ECT seizures are better at identifying differences in electrode positions than cognitive side effects, which likely co-vary with seizure characteristics based on electrode placement.

It is important to note seizure data from bipolar patients obtained from the large open-label trial were excluded from analyses. Differences in ictal EEG frequency characteristics have been identified in patients with unipolar and bipolar depression (Wahlund et al, 2009). While these differences tend to normalize over the duration of treatment, we did not note any differences in seizure characteristics from baseline to the last treatment. Unlike ECT, it could be that normalizing the EEG may not occur for patients treated with MST. Due to the novelty of predicting MST treatment outcome from seizure characteristics, it was important to maintain a clean sample, so bipolar patients were excluded from analysis at the risk of misidentifying differences in seizure characteristics related to treatment outcome opposed to differences evoked by different patient subgroups. However, it is still a worthwhile exploration to determine if these relationships with treatment outcome are maintained in different patient samples.

Additionally, although frontal MST was effective in the present study, this is a novel site of stimulation and the results from the current project may not be entirely transferrable to patients receiving vertex stimulations. The vertex stimulation target grew in popularity due to the lower seizure threshold over the motor cortex, and therefore, lower seizure thresholds at the vertex. This was favourable to frontal stimulation as previous devices with lower coil amplitudes count not consistently induce seizures when directly stimulating the frontal regions. The most up to date
MST device (MagPro MagVenture) produces magnetic fields approximately 2 times that of the original technology, and now that technological advancements have made reliable seizure induction at the prefrontal cortex a reality, it may not be necessary to continue stimulation interventions at this location. However, researchers may also have serendipitously stimulated networks involved in depression by stimulating their projections. It is therefore important to compare treatment outcome between patients receiving stimulation to the vertex opposed to the frontal cortex to ensure the prefrontal cortex is the most appropriate target for intervention.

**Study Conclusions**

In summary, the optimal parameters for MST in depression are still in the early stages of being established. The results of this study suggest that stimulations at 50 Hz induce longer-lasting MST seizures, and thus, may be better at inducing therapeutic response. However, it is important to note the ictal differences in MST frequency (motor duration, slow-wave duration, total EEG duration, and overall seizure adequacy as defined by ECT EEGs) were not related to treatment outcome. As such, the role of MST frequency in therapeutic mechanisms may not be clinically meaningful. However, these results do support the hypothesis that 50 Hz frequencies can induce seizures at lower thresholds, which may optimize MST treatment for individuals who require stimulations above the device capacities. Ultimately, randomized studies with larger samples will help to establish definitively the optimal frequency and pulse number for MST, against both electrophysiological markers and clinical outcomes in depression are warranted.

Finally, this study suggests polyspike duration and slow-wave amplitude may prove useful in identifying individuals who are likely to respond to treatment early in a treatment course. This study suggests differences in markers of seizure adequacy in MST and ECT are robust, and clinical methods of determining seizure quality should be adjusted in MST.
Future Directions: Elucidating Mechanisms of Action

The present study helped to identify predictors of treatment outcome, and coupled with existing MST work, may also shed light on its biological mechanisms of action. We will now review our current knowledge of MST to develop hypotheses about the mechanisms underlying MST’s therapeutic efficacy.

Insights from Previous Devices

Insights from simulation studies can help determine what parameters have been changed across devices, and how these changes may affect treatment outcome. When examining the electric field strength of neuromodulating devices, there are two primary measures used to explain the shape of the generated electric field. Topographic mapping is a common method of displaying the shape, strength, and spread of a stimulus, and can provide insights into the biological action of stimulations with different parameters.

Directly Stimulated Brain Volume

The minimum electric field strength required to depolarize most neurons in the brain area (≥90% of neurons) is considered a sufficient electric-field strength to “directly stimulate” that brain area. It has been suggested parameters of the stimulation pulse, namely, pulse shape, pulse width, and stimulation amplitude, affect the total brain volume directly stimulated by the magnetic pulse. (Deng et al, 2011), and altering these parameters can modify the amount of directly stimulated brain tissue.
Stimulation Spread

The second measure of stimulation shape is the spread of a stimulus, defined as the total brain volume that causes neural activation of $\geq 50\%$ of neurons. In contrast to direct stimulation, stimulation spread can only be altered by hardware and positioning of the coil, such as its’ shape and size, spacing between the coils, or varying placement of the coil to tissues with lower stimulation thresholds (i.e. vertex instead of frontal stimulation). As such, technological developments are often required to alter these parameters for clinical investigations. Currently, the twin-coil is the only approved MST-coil for the MagVenture MagPro MST device, and thus, few novel investigations can be conducted to evaluate stimulation spread of the new device. However, the twin-coil permits the adjustment of spacing between the coils, which can be used to change the depth to spread ratio of the stimulation.

Comparisons Between Generations of Devices

While previous studies demonstrated that MST stimulates only 8% of cortical neurons above activation threshold relative to ECT, which stimulates up to 98% of intracortical neurons above activation threshold. Older devices were used to model these simulations, including the theta stimulator and both the circular and double cone coils. Technological advancements made between the third and fourth generation of MST devices are great, and it may be unwise to extrapolate the information gained from this research study to the new devices.

The 3\textsuperscript{rd} and 4\textsuperscript{th} generation coil types have different internal and external diameters, spacing between coils and numbers of windings, making their induced electrical fields in the brain almost incomparable. Additionally, the magnetic field strength the MagPro can induce far outweighs that of the theta stimulator, future research using
updated MST models are required to fully understand how the current device settings influence the brain. The intensity of the MagPro stimulator is so great that even at 100 Hz, the coil amplitude and generated magnetic field is still larger than that of the theta stimulator, thus theoretically, consistent seizures should be able to be induced with stimulations at least of equal intensity to the theta device. It is thus feasible to conduct an experiment which isolates the effect of frequency from coil intensity, which will help developers understand whether increasing the magnetic field strength beyond the current maximum amplitude of the MagPro is even a worthwhile task.

Deng and colleagues conducted a spherical simulation of different coil spacing for the twin coil (Figure 11) and demonstrated that increasing the distance between coils from 90 to 110 degrees increases the spread of the stimulation spread.
Consequently, this results in a deeper and wider electric field. The Magstim double cone coil used in 3rd generation device, the theta stimulator, was fixed at 100 degrees. As such, the spread of the electric field was also fixed. Despite simulating the 4th generation twin coil device at 100 degrees, the stimulated e-field maximum strength affected approximately 2.3 times the brain volume relative to the double cone coil. (Deng et al, 2013b). Specifically, the double cone coil having a depth of 1.98 cm before less than 50% of neurons are activated, and spread of 34.0 cm² of the total brain volume stimulated above 50% neural activation threshold. while the twin-coil had a depth of 2.49 and a spread of 78.3 cm².

Additionally, previous work demonstrated only 8% of the brain volume was stimulated above activation threshold, suggesting the twin coil at 100 degrees stimulates approximately 18.4% of the brain above 50% of the neural activation threshold. To our knowledge, peer review publications accounting for all the varied parameters between third and fourth generation devices have not yet been conducted, and as such, hypotheses can only be formed by combining information from the literature with the parameters of stimulation for each device.

Device Parameter Differences

While explicit information about the internal amplitude of both coils have not been released, the 3rd generation device induced a magnetic field of 1.2 tesla, while the 4th generation induces a magnetic field of 2.75 tesla per coil. Additionally, the double-cone coil had 7 turns/wing, which the twin coil has 15 turns/ coil. These device differences correlate strongly with the ability to increase current amplitude in the coil, and as such, one can infer the amplitude in the coil is higher in the MST twin coil than the double-cone coil. As previously stated, increasing the coil amplitude is one method of increasing the volume of brain tissue that is directly stimulated.
While the pulse widths do not differ greatly, the pulse width of the double cone coil is 0.4 ms, while the twin is 0.38 ms. Minute differences in pulse width should not have a significant effect of stimulated brain volume, increased pulse widths should theoretically increase the brain volume stimulated. The new MagVenture MagPro device is capable of emitting longer pulse widths, however as this device is biphasic, doing so would reduce the amplitude of the stimulus inside the coil. As such, there may be an optimal pulse width to amplitude ratio which would maximize the direct brain volume stimulated.

**Insights from FEAST ECT**

FEAST ECT is a novel form of treatment which makes use of modifications to device settings (opposed to waveform parameters) to reduce the brain volume directly stimulated. This results in minimal cognitive side effects comparable to MST. However, the focality of the stimulation is comparable to other ECT configurations, including bi-temporal electrode placements, which is to say 90% of the brain is stimulated in such a way to cause action potentials in over 50% of the neurons. While still in its early stages, a clinical trial investigating the efficacy of FEAST-ECT induced remission and response in 55% and 65% of the patient sample (n=20) respectively, with no subjective reports of cognitive side effects or decreased neurocognitive function.

As a minimal amount of brain volume is directly stimulated, but the entire brain experiences extracellular changes in membrane potential, it may suggest minimizing the direct electrical current to brain regions involved in depression, while inducing smaller potential changes in other regions, may help maximize the benefit and minimize the cost of ECT treatment.
This result may be due to the shunting of electrical current to all areas of the brain, and the focality of stimulation cannot be readily adjusted in ECT. However, by varying parameters of magnetic stimulations, we may be able to closely replicate the e-field properties of FEAST-ECT in MST.

How Seizure Characteristics May be Affected

For instance, increasing the spread of the stimulation by increasing the spacing between coils, changing the geometric properties of the coil, as well as altering the placement of the coil may help to induce such changes. With current device settings, increasing the distance between the coils could potentially create deeper electric fields with larger spread, to activate the HPA axis, induce larger GABAergic responses from the diencephalon. Doing so would provide a multi-modal method of targeting different biological issues in depression while minimizing the cognitive side effects. Consequently, this may also increase post-ictal suppression of MST seizures, which may be used for markers of “deep MST” treatment outcome.

Limitations to Understanding MST Mechanisms of Action

ECT vs MST Seizure Threshold Comparisons

While ECT and MST have been given to the same individuals, reports of their equated seizure thresholds have gone without publication. Indeed, within-subject comparisons in seizure threshold in ECT and MST would have been a useful addition to these publication (Lisanby et al, 2003a). Having this information available would make it easier to determine the extent to which the stimulation in MST must exceed the seizure threshold, as current researchers have not yet formed a consensus.
Comparisons between ECT and MST Dosing

“Charge” in microcoulomb (mC) is the current metric of choice to describe dosage in ECT and represents the total amount of electricity delivered in one electrical stimulation. However, this method of dosing has been heavily criticized (Peterchev et al, 2010), as it combines several aspects of the ECT stimulation to determine the total amount of energy required to induce a seizure. Due to the properties of magnetic fields, a cumulative dosing metric is not possible, as the total charge delivered cannot be summated. Indeed, a cumulative metric allowing for comparison across individuals and treatment types is clinically invaluable, yet using charge as a dosing metric renders useless if multiple parameters of stimulation differ from one comparison dose to the next. As such, stimuli with the same charge can have very different parameters, and one charge using certain parameters may under- or overestimate the adequate stimulus intensity for the patient. As such, stimuli with equivalent charge can have very different clinical effects. We argue that the inability to utilize a cumulative metric is therefore a positive change in the way we think about convulsive therapy dosing.

Conclusions

Insights from previous studies, coupled with the results of the present study, demonstrate the unique ability of each MST parameter to modify the stimulation, and thus, modifies aspects of treatment. Continued explorations into modifying stimulus parameters can help to maximize the efficacy while retaining the cognitive side effect profile of current MST. Further insights into the clinical benefits of each stimulation parameter await future research.
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