# Accelerated Intermittent Theta-Burst Stimulation:

# Future Paradigms in Neuropsychiatric Disorder Treatment

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## Abstract

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*Background*: Accelerated intermittent theta-burst stimulation (aiTBS) is a novel form of non-invasive repetitive transcranial magnetic stimulation (rTMS), used in treatment resistant depression (TRD). A recent release of open label results from the Stanford Accelerated Intelligent Neuromodulation Treatment (SAINT) aiTBS paradigm have demonstrated initial efficacy in the treatment of TRD among rTMS naïve, rTMS non-responders and ECT non-responders; however, post-treatment antidepressant durability (time to relapse) and associated predictors of durability remain unexplored.

*Objective*: The objective of this study was to investigate antidepressant durability among individuals with TRD who responded (≥50% reduction in depression scores) to a series of SAINT aiTBS. A second objective was to explore factors predicting durability (e.g. prior rTMS

non-response, treatment refractoriness using the Maudsley Staging Method, or baseline depression severity). A third objective was to assess durability in the sub-group of individuals who received a second aiTBS treatment series after depressive symptom worsening or relapse occurred during the 6-month post-SAINT follow-up time-period.

*Methods*: A secondary analysis was conducted on existing data that were extracted from an online data storage tool (Research Electronic Data Capture-REDCap). The sample consisted of 33 individuals with unipolar or bipolar TRD who received 10 daily sessions (10 minutes per session with 50-minute intervals between sessions) of outpatient aiTBS over the course of 5 days, for a total of 50 sessions. Included in the durability study were anti-depressant responders (n=32) who either 1) received one series of SAINT and were followed for up to 6 months post aiTBS treatment (n=16), or 2) experienced symptom worsening (n=15) or partial response (n=1) and received a retreatment series and were followed for up to another 6 months. One participant did not respond to treatment and was excluded from the durability analyses. The primary antidepressant durability outcome measure was the Hamilton Depression Rating Scale (HDRS-6), which was administered pre/post treatment and at follow-up weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 22, and 24. The 17-item Hamilton Depression Rating Scale (HDRS-17) and Montgomery-Asberg Depression Scale (MADRS) were used as secondary depression outcome measures and were administered at pre/post treatment, and follow-up weeks 1, 2, 4, 6 and 8. A secondary aim assessed antidepressant durability and relationships between level of treatment refractoriness (Maudsley Staging Method-MSM) and baseline depression severity (MADRS). Kaplan-Meier survival analyses were used to assess durability up to 24-weeks post SAINT acute and retreatment series time-points. Univariate Cox regression analyses were used to assess associations between post-SAINT anti-depressant durability and potential covariate predictors

including 1) clinical (e.g. level of treatment refractoriness, baseline depression severity and day of treatment response), and 2) demographic (e.g. age, sex, illness duration) covariates.

*Results:* The average time to relapse across all participants completing an acute series of SAINT was 14.37 weeks (SE=1.84). Prior rTMS non-responders (n=11) showed a significantly shorter time to relapse (mean=8.46 weeks, SE=2.73 p=.006) than rTMS naïve participants (17.76 weeks, SE=2.11). Among all participants completing the acute SAINT series of aiTBS, 94% (29) were responders at 1-month, 58% were responders at 3-months and 13% were responders at 6-months. All re-treated participants (16/16) reached euthymia within the 5-day retreatment period with a mean of 14.59 weeks (SE=2.56) of anti-depressant durability. Greater baseline depression severity (MADRS) score was associated with longer durability, though this was not a significant predictor of antidepressant durability. The MSM was a significant predictor of durability.

*Conclusion:* Participants who responded to the SAINT intervention without re-treatment rTMS tended to relapse after approximately 3 ½ months. Acute series antidepressant response and baseline treatment refractoriness may be predictors of aiTBS antidepressant durability. SAINT may be a less invasive and more cost-effective option for individuals with TRD, compared with standard rTMS and ECT methods. Further research is needed to explore accelerated iTBS paradigms, the use of retreatment vs maintenance rTMS to increase durability and predictors of anti-depressant response and durability.

## Table of Contents

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## List of Figures

## List of Tables

**List of Abbreviations**

aiTBS- Accelerated iTBS
DBS- Deep Brain Stimulation
ECT- Electroconvulsive Therapy
FC- Functional Connectivity
fMRI- Functional Magnetic Resonance Imaging
HDRS- Hamilton Depression Rating Scale
iTBS- Intermittent Theta-Burst Stimulation
LDLPFC- Left Dorsolateral Prefrontal Cortex
LMM- Linear Mixed Modeling
MDD- Major Depressive Disorder
MADRS- Montgomery-Asberg Depression Rating Scale
MSM- Maudsley Staging Method
NDRI- norepinephrine-dopamine reuptake inhibitor
QIDS- The Quick Inventory of Depressive Symptoms
rs-fMRI- Resting State Functional Magnetic Resonance Imaging
rTMS- Repetitive TMS
RDLPFC- Right Dorsolateral Prefrontal Cortex
ROI- Region of Interest
SAINT- Stanford Accelerated Intelligent Neuromodulation Treatment
SCC- Subgenual Cingulate Cortex
SNRI- Selective Norepinephrine Reuptake Inhibitor
SSRI- Selective Serotonin Reuptake Inhibitor
TCA- Tricyclic Antidepressants
TMS- Transcranial Magnetic Stimulation
TRD- Treatment Resistant Depression
VNS- Vagus Nerve Stimulation

## Definition of Terms

**Adequate dose and duration***- An oral dose that is close to the manufacturer's recommended maximal dose over at least that manufacturer's recommended period of time (e.g., 300 mg/day for 6 weeks)

**Treatment Resistant Depression or Treatment Refractory Depression (TRD)**- used interchangeably in this study and are used as such in depression treatment literature. These terms do however carry distinct definitions, defined as follows.

**Treatment resistance**- in the context of this study is defined as a failure to achieve clinical response (≥50% reduction in depression) or remission (relief from depression symptoms qualifying in "normal" range of depression scales used) after an acute trial of first line psychopharmacology

**Treatment refractoriness**- treatment refractory is defined under the criteria of the Maudsley Staging Method (MSM) which utilizes a scoring method related to dimensions including 1) current depressive episode duration, 2) symptom severity (at baseline), treatment failures of 3) antidepressants and 4) augmentation medications, and 5) prior electroconvulsive therapy utilization (Fekadu et al., 2009). Drugs considered must be used in an adequate dose for an adequate time period as noted by the manufacturer's suggestion

**Treatment non-response***- A response that is poor enough with significant residual symptoms that a change in the treatment plan is called for (e.g., failure to achieve at least a 50% reduction in the HRSD score)

**Treatment response***- A response that is good enough that a change in the treatment plan is not usually called for (e.g., at least a 50% reduction in HDRS score)

**Remission-** Attainment of a virtually asymptomatic status (e.g., HDRS ≤7) for at least 2 consecutive weeks

**Relative treatment resistance***- Non-response to an adequate dose of a potentially effective medication for an adequate length of time

**Absolute treatment resistance***- Failure to respond to a maximal trial of a single treatment for an extended period of time
(e.g., imipramine at 300 mg/day for 6 weeks)

**Treatment-refractory depression***- Treatment non-response (i.e., persistence of significant depressive symptoms) despite at least two treatment trials with drugs from different pharmacological classes, each used in an adequate dose for an adequate time period

**Mechanism of Action (MOA)-** the specific biochemical or biological interaction through which a drug or other intervention produces its pharmacological or mechanistic effect.

**Medication intolerance***- At least 4 consecutive weeks of treatment, during which the patient has had an adequate dose for at least 3 weeks with an inability to achieve or maintain an adequate therapeutic dose of an antidepressant drug due to idiosyncratic reactions or side effects

**Partial Response-** A response that shows 25-49% reduction in depression scale scores either during or at the end of a treatment series, which may be measured at multiple time-points.

*(Thase & Rush, 1995)

# Chapter 1: Introduction

The purpose of this chapter is to provide an overview of depressive disorder prevalence with an emphasis on treatment resistant depression (TRD) and the use of repetitive transcranial magnetic stimulation (rTMS) for symptom management. The problem statement, purpose, aims and hypotheses of this study will then be summarized.

## Overview

Major depressive disorder (MDD) has a national, lifetime prevalence of approximately 20.6%, carrying the largest economic burden of disability in the United States (Brody, 2018; Kessler, 2012). With an 18.4% growth in depression prevalence between 2005 and 2015, further developing treatment paradigms for depression is an important public health concern (Ferrari et al., 2013a; Ferrari et al., 2013b). Due to the episodic nature of depression, a significant proportion of those who receive first line treatment for depressive symptoms in primary care and psychiatric settings continue to experience depression, or subsequent depressive episodes, with a substantial proportion never achieving anti-depressant response or remission (Rush et al., 2006; Souery et al., 2007). Additionally, MDD increases suicide risk with a lack of response and/or access to available treatment options in psychiatric medications and adjunct therapies, resulting in poor outcomes and unwanted effects (Bergfeld et al., 2018; Gibson et al., 2010; Rush et al., 2006). Individuals who do not respond to traditional methods may ultimately be referred to receive electroconvulsive therapy (ECT) as the "gold standard" for treatment resistant depression (TRD); however, relapse may occur as early as 1week post-ECT (Jelovac et al., 2013). Although studies have shown other neuromodulatory paradigms may be as effective as ECT, with more favorable safety and comparable efficacy, periods beyond short-term (e.g. 1-month) durability data are lacking across paradigms (Magnezi et al., 2016).

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive, US Food and Drug Administration (FDA) approved neuromodulatory treatment, now widely used for treatment resistant depression (TRD) (Brunoni et al., 2017). Despite the many milestones achieved in refining rTMS treatment parameters and paradigms over the last three decades, inter- and intra-individual variation in anti-depressant response and the cumbersome nature of multiple treatment sessions over many weeks, highlight the need for further exploration in individualizing and optimizing rTMS treatment for TRD. A recent non-inferiority trial deemed a newly re-introduced, patterned form of rTMS called intermittent theta-burst stimulation (iTBS) equally as efficacious in a fraction of the time required for antidepressant response as compared with conventional rTMS (Blumberger et al., 2018). Additionally, the use of accelerated rTMS protocols have become more readily utilized and assessed to potentially increase the speed by which antidepressant effects can begin (Baeken et al., 2019). While literature supports the efficacy of rTMS and iTBS paradigms, much less is known about antidepressant durability (time to relapse) and which strategies to use for maintaining anti-depressant effects among those who respond to rTMS treatment. Additionally, further assessing potential predicting factors of anti-depressant durability is an area deserving of more attention.

**Problem Statement**

Although prior research, including the parent study data of this sample, supports the preliminary effectiveness of a novel, accelerated intermittent theta burst stimulation (aiTBS) protocol called the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT), little is known about the long-term antidepressant effects post-aiTBS in a TRD population. To date, no data exist related to the antidepressant durability of this specific aiTBS protocol, covariate factors potentially associated with anti-depressant durability outcomes, and the response to

reintroduction after responding to an initial aiTBS treatment series. Therefore, this study provides the opportunity to explore an area of antidepressant durability and retreatment within a new rTMS treatment paradigm for TRD, while also answering questions related to clinical and demographic factors that may be associated with antidepressant durability.

**Study Purpose**

As the parent study sought to assess antidepressant efficacy and feasibility of the SAINT protocol for TRD including a subgroup of prior, conventional rTMS non-responders, these results indicated that a novel, accelerated, targeted, high-dose rTMS protocol may provide 90% antidepressant response and remission rates in a difficult to treat population (Cole et al., 2019). Additionally, the use of retreatment for those experiencing symptom worsening was also explored, reporting similar response and remission trends. With the novelty of the SAINT paradigm and lack of data reporting antidepressant durability and maintenance of these antidepressant effects, the purpose of this study was to explore the antidepressant durability outcomes after an acute series of aiTBS (SAINT). Secondarily, covariates/predictors of antidepressant durability were also explored. Finally, antidepressant durability was also assessed in the subgroup of participants who were retreated with a second series of aiTBS upon depressive symptom worsening or relapse during their 6-month post-SAINT follow-up.

**Study Aims & Hypotheses**

The specific aims of this study were to:

1) Assess and describe the antidepressant durability (time to relapse) after a novel, aiTBS (SAINT) paradigm in a TRD group, using the clinician-rated HDRS-6 depression measure at post-treatment weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24, while assessing group differences (i.e. prior rTMS non-responders).

Hypothesis:

1.1 Participants who previously did not respond to a conventional series of 4-6-week rTMS will experience early relapse compared with the rTMS naïve participant group.

2) Explore the relationships between durability (time to relapse) and a) day of response/remission (day 1, 2, 3, 4 or 5 of acute aiTBS), b) treatment refractoriness (Maudsley Staging Method) and c) baseline depression severity (using the MADRS, confirming with HDRS-6).

Hypotheses:

2.1 Greater length in durability will be associated with earlier response during the 5-day SAINT treatment series.

2.2 Treatment refractoriness (i.e. Maudsley Staging Method) will have a stronger association with antidepressant durability than baseline depression severity.

3) Assess the anti-depressant durability (time to relapse) of a second aiTBS treatment series for those who relapsed during the 6-month period.

Hypothesis:

3.1 There will be similar response durability between first and second aiTBS treatments after a previous antidepressant response, for those who experienced symptom worsening (≥25% depression score increase) or relapse and underwent a SAINT retreatment series.

# Chapter 2: Review of Literature

The purpose of this chapter is to review the relevant clinical and diagnostic criteria of depressive mood disorders, including standard treatment approaches. This will additionally focus on the literature surrounding rTMS for mood disorders, with specific emphasis on rTMS for TRD, as the utilization of rTMS among other disorders may be clinically assessed and managed with a different approach. Additionally emphasized is the importance of anti-depressant durability related to current and developing depression treatment methods. The embedded dissertation study will particularly focus on the antidepressant durability and retreatment durability among those who have responded to a novel rTMS treatment protocol, accelerated intermittent theta burst stimulation (aiTBS) for TRD, and will include the supporting theories underpinning the development of this paradigm. Finally, the implications of these findings will be discussed in the context of future rTMS maintenance and retreatment strategies.

## Depressive Mood Disorders

In a given year, approximately 8.1-9.5% of American adults have a diagnosable mood disorder with a worldwide, lifetime prevalence of nearly 30% (Brody, 2018; Kessler, Chiu, Demler, & Walters, 2005; Steel et al., 2014). Depression-related mood disorders carry the heaviest burden of disability in the US with great social and economic burden (Kessler, 2012; WHO, 2008). Mood disorders are discussed in more detail for the purpose of this study as individuals with both unipolar and bipolar depression were included in these open label aiTBS trial data (Cole et al., 2019). Depressive disorders in this review are based on criteria encompassing a diagnosis of either MDD, treatment resistant depression (TRD), unipolar TRD or bipolar TRD in a current depressive episode as identified in the Diagnostic and Statistical Manual of Mental Disorders, DMS-5 (American Psychiatric Association, 2013). Additionally,

both current and previous (DSM-IV) diagnostic criteria are discussed to give more clinical context of individuals who were included in this study. Note the use of the American Psychiatric Association (APA) versions cited below, which are included to outline the criterion considered when assessing clinical history and current symptoms of the participants included in this study.

*Clinical Criteria*

Mood disorders are separated into two primary categories of "depressive disorders" and "bipolar and related disorders," as defined by the current Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), whereas the prior DSM (DSM-IV-TR) referenced these in the same overarching category of mood disorders (American Psychiatric Association, 2000; American Psychiatric Association, 2013). The current DSM stresses the difference between them as issues in duration, time and presumed etiology. Depressive disorders encompass a variety of severity levels and subtypes. Major depressive disorder (MDD), used interchangeably with major depression, unipolar depression or clinical depression, is identified as a significant impairment in social and/or occupational functioning indicated by 5 or more of the following persistent symptoms of depression occurring over a period of two weeks (must include either item 1 or 2) (DSM-5 criteria):

1. Depressed mood most of the day, nearly every day
2. Loss of pleasure most of the day, nearly every day
3. Change in weight or appetite nearly every day, not due to dieting
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day
6. Fatigue or loss of energy nearly every day
7. Feeling worthlessness or excessive or inappropriate guilt nearly every day

8. Reduced ability to concentrate, or make decisions, nearly every day
9. Recurrent thoughts of death or suicide

When recording an MDD diagnosis according to the current DSM-5 (American Psychiatric Association, 2013), the following aspects are listed in order: MDD, single or recurrent episode, severity/psychotic/remission specifiers, additional specifiers without application to the current episode. A more chronic form of depression, persistent depressive disorder (PDD) or "dysthymia," may be diagnosed if the mood disturbance continues for a minimum of 2 years but with less depressive symptom severity. PDD includes chronic major depression and dysthymia criteria as previously included in the prior DSM-IV (American Psychiatric Association, 2000). Specifiers on MDD include "with mixed features" and "with anxious distress" to allow for the presence of manic symptoms as a part of the depression diagnosis when full manic episode criteria are not met, and when the presence of anxiety in patients may affect overall prognosis, treatment and patient response, respectively. Other specifiers relate to melancholic, psychotic, catatonic peripartum or seasonal pattern features. Other depressive disorders of note, included in the previous diagnostic manual, DSM-IV-TR (American Psychiatric Association, 2000), are melancholic (loss of pleasure or reactivity) depression, psychotic major depression, catatonic (e.g. mutism, stupor or dazed state) depression, postpartum depression, perinatal depression, premenstrual dysphoric disorder, seasonal affective disorder, dysthymia, double depression (MDD and PDD/Dysthymia), depressive personality disorder (removed from DSM but considered between periods of depressive episodes), recurrent brief depression and minor depressive disorder.

The DSM-5 differentiates depressive disorders from bipolar disorders (sometimes referred to as "manic depression") in that those with depressive disorders maintain or experience

cycles only of depressed states from an individual's baseline, whereas individuals with bipolar disorders experience at least one maintained or episodic period of either both depressive (low mood) and manic or hypomanic (high mood) symptoms, or manic symptoms alone (American Psychiatric Association, 2000). The most commonly referenced bipolar disorders refer to two types, Bipolar I and Bipolar II. Bipolar Type I is differentiated by a history of one or more manic or mixed episodes and does not require but typically includes a depressive episode (or series of depressive episodes). Bipolar Type II includes symptoms of at least one episode of hypomania and at least one major depressive episode. If one meets criteria for a full manic episode, they would then meet criteria for Bipolar Type I. Cyclothymia encompasses chronic, sub-threshold severity in mood swings and hypomanic symptoms of bipolar disorder and is less common but may result in a future diagnosis of Bipolar I or II. Unspecified bipolar disorder subtypes may be employed when similar symptoms do not meet full criteria for the other subtypes or there is an additional presence of symptoms not found in the two primary bipolar types, such as psychosis or peripartum onset (American Psychiatric Association, 2013). Additionally, across all bipolar disorder subtypes (excluding psychosis), individuals experience more depressive than manic episodes, and a longer duration of depressive episodes, with few symptom management options (Tondo et al., 2017).

*Depression Severity and Refractoriness*

Depression severity is commonly used as a baseline measure to determine individual appropriateness or entry criteria for treatment based on depression scale cut-off categories (e.g. mild, moderate, severe and very severe depression scale cut-offs). Due to the fluidity and inherent fluctuation in such scales, others such as Fekadu and colleagues (2009) have explored additional ways that may be better predictors of appropriateness and response to treatment. The

conceptualization of depression treatment "resistance" or "refractoriness" has been utilized interchangeably with "severity"; however, this study utilizes distinct delineations between these concepts to show the multi-faceted components excluded from baseline severity that may be important in predicting response to rTMS treatment. Treatment resistance in the context of this study, as utilized in seminal TMS studies, was defined as a failure to achieve clinical response (≥50% reduction in depression) or remission (relief from depression symptoms qualifying in "normal" range of depression scales used) after an acute trial of first line psychopharmacology (Thase & Rush, 1995). Thase and Rush (1997) went on to develop a staged method for assessing anti-depressant resistance including the failure of electroconvulsive therapy (ECT); however, this may not fully capture other aspects of treatment resistance such as depression chronicity, severity, etc.

In order to more fully conceptualize "refractoriness," the Maudsley Staging Method (MSM) was utilized to encompass 5 factors (current depressive episode duration, level of depression severity, antidepressant failures, augmentation medications, and ECT failure) that have been significantly associated with greater levels of depression treatment resistance observed over time (Fekadu et al., 2009). Criteria for participation in the parent study included treatment resistance after the failure of at least one antidepressant medication and consideration of the additional four factors, in order to create an overall refractoriness score out of a maximum of 15 points (see Appendix A). The MSM was utilized in the parent study (Cole et al., 2019) to develop a minimum criterion for inclusion (≥8) among participants, though two participants were included in this study with an MSM score of 7 in order to assess a wider range of severity from moderate to severe.

## Depression Pathophysiology

### *Monoamine Hypothesis*

The monoamine hypothesis is considered to be the classic biological theory of depression; this created a simplistic basis for antidepressant medications targeting neurotransmitters such as serotonin, dopamine, norepinephrine and epinephrine (Delgado, 2000). This hypothesis was supported by showing deficits in specific neurotransmitters that control various functional attributes corresponding to symptoms of depression. For example, serotonin has shown to regulate mood, sleep appetite, memory and overall functioning while norepinephrine has been associated with energy, alertness, attention and concentration as well as focus (Nutt, 2008). Over the years, antidepressant medications have targeted these neurotransmitters in an attempt to increase the cellular interaction and transmission also thought to strengthen their synaptic signaling (Delgado, 2004). Despite being the most widely accepted understanding of mechanistic action associated with mood disorders, the monoamine hypothesis has undergone much scrutiny for its over-simplicity and lack of explanation as to the delayed onset of reaction upon use of antidepressants (Boku, Nakagawa, Toda & Hishimoto, 2018). As continued research has taken shape, it is clear that depression and other symptoms of mood dysregulation are not simply explained by their relationships with monoamines, resulting in other potential models of mechanistic action and how symptomology may be a more complex product ranging from cellular dysfunction to neuronal circuitry.

*Connectivity Models of Neural Circuitry*

Methodological advancement (e.g. functional brain imaging and electroencephalography) in recent years have expanded the development of understanding psychopathology beyond a single mechanism (Pandya et al., 2013; Williams, 2017). Through exploring structural and functional connectivity patterns, areas impacting symptoms of depression have been attributed toward a localized abnormality in one or a few primary or secondary brain regions (e.g. dorsal and medial prefrontal cortex). Depression has historically shown associations in areas of the brain including cortical and limbic regions such as the dorsolateral prefrontal cortex (DLPFC), hippocampus and subgenual cingulate cortex (SCC) (Drevets, Savitz & Trimble, 2008; Mayberg, 2009). With some of the most reproducible, neuronal aberrations, a decrease in the SCC has been linked to a variety of therapeutic interventions for depression including deep brain stimulation and rTMS (Fox et al., 2012; Mayberg, 2009; Mayberg et al., 2007). With further exploration of brain region connectivity associated with symptoms of depression, the idea that one or a few areas alone are isolated, has become obsolete.

In recent years, large-scale connections among a variety of brain regions have been identified, which may underlie specific biotypes of processes including mood regulation, attention, perception and a range of functions such as motor, visual and auditory. In Williams' (2017) overview, six circuits are discussed as potential dysfunctions related to depression and anxiety. These circuits (default mode, salience, negative affect, positive affect/reward, attention and cognitive control) summarize current literature supporting the evidence of each internal region associated within each circuit and their potential interaction with anxiety and depression related symptoms. Williams also proposes the potential model of utilizing specific treatment modalities (e.g. TMS, DBS, therapies) to target symptom clusters. Specific to depression, these

circuits have been further delineated toward overarching clusters of symptoms linked to multiple regions: 1) elevated connectivity in the ventral limbic affective network is associated with dysphoria (excessive negative mood), 2) decreased frontal striatal reward network has been associated with anhedonia (loss of interest and pleasure), 3) default mode network connectivity has been associated with increased rumination and 4) decreased connectivity in the dorsal cognitive control network may underlie cognition deficits (Li et al., 2018). In addition to individual and small group efforts, the BRAIN Initiative and National Institutes of Health are aiming to advance and incorporate neuroscience in future diagnostic classifications for mental health challenges (Insel et al., 2010; Kupfer & Regier, 2011; Mott, Gordon, & Koroshetz, 2018). With growing evidence, there is still much to explore in relation to these large-scale networks and their associations with mood and behavior.

Decades of research and application of trial and error have revealed a variety of potential pathophysiological avenues linked to mood dysregulation and, more specifically, to depressive symptoms. The classic monoamine hypothesis in psychiatry created a foundational approach for antidepressants to target specific neurotransmitters via increasing extracellular levels and altering synaptic activity. In recent years, the body of literature expanding the complexities of neurocognitive function and mood disorders has, if anything, shown the immense gaps in literature and knowledge, while extending to exciting new areas of focus encompassing the inclusion of cell-to-cell, brain region and large-scale brain network region connectivity hypotheses. With advanced methods more readily available for use, it is becoming much more feasible to investigate these new areas of discovery and ways in which they may inform and enhance treatment for neuropsychiatric disorders such as depression.

**Depression Treatment**

First line treatment in depressive mood disorders typically starts in primary care and/or psychiatry. Psychiatric medications such as antidepressants may be combined with adjunct therapies such as psychotherapeutic interventions as a secondary recommendation; however, in up to 30% of individuals with major depression, first line treatments will not work (Keller, 2005; Thase & Rush, 1995). The largest, longitudinal depression treatment study to date (Sequenced Treatment Alternatives to Relieve Depression - STAR*D) found a significant, decreased likelihood of response to the next line of treatment after every treatment failure experienced (Rush et al., 2006). Additionally, individuals with chronic or long-term symptoms of depression tend to be more resistant to treatment than those with acute depressive episodes (Dunner, 2001). For individuals with TRD in which adequate doses of antidepressants and augmentation medications in combination with other therapeutic interventions do not show improvement, neuromodulatory or other more invasive interventions may be suggested (Holtzheimer & Mayberg, 2012).

In TRD populations, electroconvulsive therapy (ECT) has predated psychiatric medications and continues to be the "gold standard" of treatment in these populations (Kellner et al., 2006; Sackheim et al., 2001). ECT and other ablative neurosurgical techniques such as deep brain stimulation (DBS) and vagus nerve stimulation (VNS) have been utilized for more refractory depression with limitations; however, their debilitating side-effects (e.g. memory loss, confusion, nausea or medical complications) are less than desirable (Holtzheimer et al., 2017; Muller et al., 2018). As neuromodulation techniques such as transcranial electrical stimulation (tES) and repetitive transcranial magnetic stimulation (rTMS) have developed as a "third pillar" in psychiatric treatment for depression, rTMS has recently been touted as a potential alternative

for ECT as methods are refined and further tested among those who are ECT non-responders (Cristancho et al., 2013; Polania, Nitsche & Ruff, 2018). With new rTMS paradigms and approaches precipitously expanding, its use in managing TRD symptoms continues to refine and develop alongside novel techniques and methodological advances (Baeken et al., 2019).

**TMS Overview**

Non-invasive Brain Stimulation (NIBS) is an overarching term for neuromodulatory modalities developed to better understand the brain's associations with cognition, emotion and behavior. In recent years, both electromagnetic and electrical stimulation have built foundations in advancing areas of biological and clinical settings with interventions such as transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES) (Polanía et al., 2018). The focus here is on the history of TMS, which has rapidly developed as a diagnostic and treatment tool in psychiatry.

Based on Faraday's law of induction, the primary element of TMS operates upon the activation of a fluctuating magnetic field (1-3 Tesla) causing an electrical current to flow from a coil to a nearby conductor such as neural tissue (Hallett, 2007). First demonstrated by Barker and colleagues (1985) in a single pulse TMS device, stimulation over the motor cortex caused muscle contraction of the limbs, whereas visual cortex stimulation produced flashes of light (phosphenes) with closed eyes. Upon the investigation of TMS as clinical tool when utilizing repetitive pulses over a period of time to perturb neural circuitry, the clinical applications of repetitive TMS have further developed. Since FDA-approval in 2008 where the NeuroStar TMS Therapy System (Neuronetics, Malvern, Pennsylvania; 510 K number: K083538) was cleared as the first rTMS device, 4 additional devices have been approved including the Brainsway Deep TMS System (Brainsway, Har Hotzvim, Jerusalem; 510k number: K122288), the Rapid Therapy

System (Magstim, Philadelphia, Pennsylvania; 510k number: K143531), the MagVita Therapy System (MagVenture, Atlanta, Georgia; 510k number: K150641), and the NeuroSoft TMS (TeleEMG, LLC, Los Angeles, California; 510k number: K160309).

Single pulse TMS (SP-TMS) has been used to send short bursts of action potentials in order to perform both diagnostic and task performance evaluation. For example, TMS over the Broca's areas can arrest speech, while stimulation over the visual cortex may suppress conscious visual perception when applied at a specific time after the visual stimulation is displayed (Farzan, 2014). SP-TMS has also been used in conjunction with advanced methods such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) to assess pulse propagation in various areas of the brain. As the current method in treatment "dosing" for non-motor areas is based on the resting or active motor threshold (MT) of the primary motor cortex (M1), action potentials and downstream effects of single pulses shown to elicit this MT can then be measured in both regions. (see Klomjai et al., 2015 for rTMS paradigms figure).

Paired pulse TMS (PP-TMS) is the sequence of two, single TMS pulses allowing the observation or measurement of corticocortical connections. For example, interrogation of motor cortical pathways has provided diagnostic and rehabilitative guidance in the assessment of stroke, while other methods may show how a sequenced pulse in one brain region may interconnect with a pulse delivered elsewhere. The implications of these methods have shed light on interconnected brain areas and network dynamics by both direct and indirect observation (Vahabzadeh-Hagh, 2014). Paired-associative Stimulation (PAS) is another example of cortical function modulation. By combining median nerve stimulation with the corresponding sensorimotor cortex area, PAS is typically used with cognitive or behavioral tasks to assess dynamic cortical plasticity engagement (Luber et al., 2017; Ragert et al., 2003; Ziemann et al.,

2008). Repetitive TMS (rTMS) is the application of multiple, frequency-based pulses delivered over a specified period of time desired to produce long term potentiation (LTP) or long-term depression (LTD) in the efficacy of neuronal synapses found in targeted areas of the brain. rTMS encompasses both high (>1Hz) and low-frequency (1Hz) pulses delivered in either continuous or repetitive patterns. This includes theta burst stimulation (TBS), which is a form of patterned rTMS that delivers rTMS at intermittent or continuous, 50 Hz bursts of patterned rTMS. iTBS will be further described in its own section, for the purposes of this study.

**rTMS Mechanistic Action**

The clinical application of rTMS has relied on the seminal findings of rTMS on motor evoked potential (MEP) amplitude which showed an increase in localized neuronal excitability from high-frequency stimulation and an inhibitory effect in low-frequency stimulation (Chen et al., 1997; Pascual-Leone, Walls-Sole, Wassermann & Hallett, 1994). This concept was further developed with auxiliary imaging showing implications for high-frequency rTMS applied over the dorsolateral prefrontal cortex region producing an antidepressant effect; however, similar effects have occurred from low-frequency stimulation, calling this method into question (George et al., 1997; Kito, Hasegawa & Koga, 2011). This jump from classical observation to clinical assumption has created a gap in the literature which continues to question the exact underlying mechanistic action of rTMS, and what may be creating mood disorder symptom relief. To fill the gaps in rTMS knowledge and development, further assessing past, present and novel rTMS paradigms will be required, including the intricate parameters that may have more bearing on outcomes that previously assumed (e.g. coil placement, targeting, dosing, frequency, etc.).

*Hebbian, Homeostatic and Meta Plasticity*

Hebbian plasticity is commonly referred to as the mechanism of neuronal coding and information storing, whereas homeostatic plasticity moves the neuronal state back to an original form (Fox & Stryker, 2017). Initially proposed by Donald Hebb in the 1940's, Hebbian plasticity has played a major role in understanding the functions of memory, learning and rehabilitation as a result of evidence supporting synaptic activity changes resulting in longer-term post-perturbation synaptic change. Synaptic plasticity is thought to carry a scale of "synaptic weight" in which cells may saturate creating a threshold for net excitatory drive and strength (Bienenstock, Cooper & Munro, 1982; Fox & Stryker, 2017). Synaptic scaling then showed the extent to which tolerable limits of synaptic excitability are maintained resulting in the discovery of homeostatic properties as a result of regulating and preserving these thresholds. Homeostatic plasticity was thus conceptualized as a result of observing mechanisms of Hebbian plasticity returning to or maintaining neuronal activity at a stable, "set" point. It is proposed that homeostatic plasticity may occur over a number of scales ranging from synaptic to cell population levels. Beyond the scope of Hebbian plasticity may be late phase neuronal plastic effects that produce structural synaptic changes. This higher order form of plasticity may be a product of the ability to prime and induce subsequent synaptic plasticity such as LTP or LTD. Overall, the exact model of how Hebbian and homeostatic plasticity interact and maintain neuronal stability both in the context of perturbation or preservation, remains under investigation.

Upon application of rTMS, Hebbian and homeostatic plasticity are thought to play a role as a result of neuronal perturbation of the desired brain region or neural circuit, while building upon the concept that "neurons that fire together, wire together" in the sense that the spaced,

repetitive nature of the rTMS paradigm allows for short and long-term effects (Karabanov et al., 2015; Lowel & Singer, 1992). A potential ceiling effect as a result of homeostatic plasticity may explain inter- and intra-individual variation in response to rTMS treatment; however, this is unclear. Further developing and investigating advanced methods related to these properties may shed light on refining rTMS paradigms across populations. More translational research is needed to explore the effects of Hebbian, homeostatic and long-term effects interacting with the neurophysiological and clinical effects of rTMS.

*rTMS and Neurotransmitters*

Similar to the effects of antidepressant medications, rTMS in the treatment of mood disorders has targeted the large concentration of serotonin and dopamine neurotransmitters found in the prefrontal cortex and deeper brain structures such as the striatum and hippocampus during animal model experiments (Gur, Lerer, Dremencov, & Newman, 2000; Pogarell et al., 2007). As the use of antidepressant medications has also been associated with the normalization of the hypo-thalamic-pituitary-adrenal axis, Keck et al. (2001) explored this mechanism with rTMS and noted a decrease in both adrenocorticotropic hormone (ACTH) and corticotrophin-releasing hormone (CRH). Additionally, works associating Parkinson's Disease with dopamine production have highlighted significant dopamine release during high-frequency stimulation over the DLPFC, which have also shown to have anti-depressant effects in this population (Cho & Strafella, 2009; Khedr, Farweez & Islam, 2003). Finally, the short and long-term impact of depression on alteration of brain derived neurotrophic factor (BDNF) concentrations and its' receptor, tropomycin receptor kinase B (TrkB), is thought to play a significant role in modulating inflammation-induced depression (Zhang, Yao & Hashimoto, 2016). Further studies are needed

to more succinctly identify the effects of both high-frequency (excitatory) and low-frequency (inhibitory) rTMS on specific neurotransmitter functions in various brain regions.

*rTMS, Neuroplasticity and Neurogenesis*

Neuroplasticity is the brain's continuous ability to adapt neurosynaptic organization, new neuronal growth and new neural connection during short-, medium- and long-term periods of time due to environmental change, injury or illness. There is little dispute of the idea that new neurons are generated in the adult brain (neurogenesis); however, recent studies have shown a wide variation in the magnitude, localization and overall functionality of this process across brain regions (Dennis et al., 2016; Sorrells et al., 2018; Spalding et al., 2013). rTMS is thought to aid in enhancing neuroplasticity as the stimulation of clustered neurons have shown to shift in ionic equilibrium which then creates a change in synaptic plasticity (Kuwabara et al., 2002). Less established but convincing results have shown links between new neural activity in the hippocampus related to learning, as well as electrical activity such as rTMS being utilized a as a perturbation mediator (Lisanby & Belmaker, 2000; Ueyama et al., 2011).

As altered neuronal activity is what is thought to aid in enhancement or new generation in an area of clustered neurons, long-term potentiation (LTP) has been a theory relating the persistence of synaptic strength as a result of rTMS stimulation (Chervyakov, Chemyavsky, Sinitsyn, & Piradov, 2015). Excitatory rTMS has shown LTP via enhancing synaptic strength for up to 6 months, whereas long-term depression employs low-frequency stimulation to decrease synaptic strength (Duffau, 2006; Purves, 2008). The molecular basis for rTMS changes in LTP may involve post-synaptic NMDA receptors containing cationic channels that are typically blocked by magnesium ions during a resting state but when depolarized, allow calcium ions into the post-synaptic neuron, ultimately creating LTP. Inversely, LTD occurs when these calcium

ions are slowed. Overall, the combination of LTP and LTD are thought to greatly contribute toward the durability and lasting effects of rTMS.

*rTMS and Genetic Expression*

For over two decades, animal studies have shown links between rTMS and changes in gene expression. Aydin-Abidin and colleagues (2008) revealed both high- and low-frequency rTMS directly altered expressions of c-Fos and zif268, immediate early gene (IEG) proteins in the limbic as well as primary motor and sensory cortices. This study found either a similar activating response between both high and low-frequency stimulation, or simply a lack of response with low-frequency stimulation but no inhibitory effects. Additionally, studies have shown patient-dependent response to rTMS linked with polymorphisms in genes encoding 5-$HT_{1A}$receptors, brain derived neurotrophic factors (BDNFs) and serotonin carriers (Cheeran et al., 2008; Zanardi et al., 2007). Finally, it is proposed that rTMS may enhance enzyme production while inducing gene expression; however further research is needed to make this conclusion (Chervyakov et al., 2015). The impact of rTMS on genetic expression has clearly shown evidence that may indicate ways in which therapeutic effects manifest, and how to further assess and enhance patient response.

*rTMS and Neuronal Preservation and Growth*

Neuroprotective mechanisms appear to be another result of rTMS as animal studies have shown an association between high-frequency stimulation and new neural growth (Ueyama et al., 2011). Active vs. sham, low-frequency rTMS has also shown to robustly increase gray matter volume when applied over the left superior temporal gyrus (May et al., 2007). Changes observed include increase in cell size, synaptogenesis, increase in blood flow and neurogenesis. rTMS has

also shown to protect against neuronal death when used with models of ischemic attack and prolonged ischemia (Fujiki, Kobayashi, Abe & Kamida, 2003).

rTMS has also shown impact BDNF concentration and its neuronal morphology (Ma et al., 2013; Muller et al., 2000; Wang et al., 2011). Of particular relevance, Ma and colleagues (2013) found that high-frequency stimulation in mouse hippocampal cell cultures induced structural lesions in neurons and reduced the number of dendrites, axons and synapses. Additionally, in patients with depression, high-frequency stimulation over the left prefrontal cortex increased BDNF concentration in 3-methoxy-4-hydroxyphenylglycol (MHPG) blood plasma which was also correlated with a decrease in depression (Yukimasa et al., 2006). It is clear that rTMS has an impact on new neuronal growth and preventing neuronal death; however, study replication and further development of research methodologies to include the assessment of various rTMS parameter impacts on neurotrophic effects among patients with mood disorders is greatly needed.

*rTMS and Brain Region Targeting*

Cortical limbic regions such as the dorsolateral prefrontal cortex (DLPFC), hippocampus and subgenual cingulate have been identified as areas corroborating reduced cerebral metabolic rate of glucose uptake and reduced cerebral blood-flow in patients with increased depressive symptoms (Drevets, Savitz & Trimble, 2008; Mayberg, 2007). Based on this theory, seminal rTMS research and the continued primary protocol in the treatment of mood disorders and TRD targets the left DLPFC (LDLPFC) with high-frequency stimulation (George et al., 1995; George et al., 1997; O'Rearon, 2007). Some have focused on low-frequency rTMS over what is thought to be an "over-active" region within the right-DLPFC, with promising results (Berlim, van den Eynde & Dakalakis, 2013). Other studies have shown abnormalities in brain regions such as the

medial and orbital prefrontal cortices, giving evidence for these methods of rTMS targeting in the treatment of depression (Dunlop et al., 2015; Fox et al., 2012; Samara et al., 2018). Further research is needed to assess whether the specific left, right or medial PFC regions produce the best outcomes for patients with mood disorders receiving rTMS. As the field of neuromodulation methodology expands, rTMS treatment for mood disorders coupled with advanced methods will continue to explore targeting areas of the brain that may be correlated to mood dysregulation and related depression symptomatology. These studies may be crucial in uncovering brain region specific symptom clusters, while also adding to future rTMS paradigm literature. Due to more recent knowledge that brain region targeting may importantly facilitate downstream effects into deeper structures, region-to-region and larger scale network targeting must be considered.

*rTMS and Large-Scale Brain Networks*

As previously discussed, the framework for understanding human brain functionality and organization has further developed the theoretical basis for emergent research focusing on large-scale brain networks, or circuits, and the potential impact of rTMS on these systems as they relate to symptomology (Bressler & Menon, 2010; Philip et al., 2018; Williams, 2016). Organized, large-scale neural networks including the frontoparietal central executive network (CEN), the medial prefrontal-medial parietal default mode network (DMN) and the salience network (SN), have been linked to psychiatric pathological functioning in depression (Fox, Buckner, White, Pascual-Leone, 2012). The DMN has been associated with self-referential processing and memory retrieval, and encompasses the medial prefrontal cortex, medial parietal region, the posterior cingulate cortex and posterior hippocampus (Raichle, et al., 2001). The CEN has been shown to hold a primary role in executive functioning and emotion

regulation with regions containing the DLPFC and lateral posterior parietal regions of the brain (Miller & Cohen, 2001). The SN is identified as encompassing the anterior insula and dorsal anterior cingulate cortex including the amygdala, ventral striatum and substantia nigra/ventral tegmental area. The SN is thought to process and synthesize sensory, emotional and cognitive information influencing communication, social behavior and self-awareness while also playing a role in regulating and mediating changes in the aforementioned DMN and CEN networks (Menon, 2015).

Liston and colleagues (2014) utilized fMRI imaging at baseline to show increased activity in the DMN and decreased activity within the CEN and minimal interaction between both regions, among patients with depression compared to healthy subjects. Furthermore, the use of high-frequency rTMS in this study appeared to normalize hyper-connectivity in the DMN but not in the CEN and induced an inversely correlated activity between the dorsolateral prefrontal cortex and medial prefrontal DMN (Liston et al., 2014). Additionally, in patients with comorbid MDD and post-traumatic stress disorder (PTSD), improvements in depression at post-treatment were predicted by more negative pretreatment connectivity between the subgenual anterior cingulate cortex (sgACC) and DMN as well as a positive amygdala and ventromedial prefrontal cortex connectivity at baseline. Reduction in depression post-rTMS was correlated with reduced connectivity between the sqACCm DLPFC, DMN and insula, and reduced connectivity between the hippocampus and insula (Philip et al., 2018).

In a review of neural structure targeting and the use of brain stimulation for psychiatric disorders, Downar, Blumberger and Daskalakis (2016) discuss the ability of rTMS to target the SN via the DLPFC more easily via the anterior cingulo-insular network (aCIN) and other nearby regions. Current methods targeting the LDLPFC are less able to reach the dACC and anterior

insula; however, the ability to perturb these regions may increase response to treatment. This is noted as a difficult approach with current stimulation technology and methods, but potentially feasible with devices that may target deeper regions of the brain such as the deep rTMS H-Coil. This would also support the target of the dorsomedial region for rTMS as some have explored with preliminary depression treatment success (Downar et al., 2013; Dunlop et al., 2015). Overall, the taxonomy and ability to create biomarkers and brain region targets based on associated symptom clusters with specific circuitry in mind, remains under investigation.

**rTMS parameters**

rTMS parameters are typically comprised of 4 primary treatment delivery factors: 1) treatment location, 2) intensity, 3) frequency and 4) duration. Treatment location is pre-determined to be the targeted area of the brain where the stimulation will be applied. In most studies of rTMS for depression, treatment is applied over the left-dorsolateral prefrontal cortex (L-DLPFC) or right dorsolateral prefrontal cortex (R-DLPFC) as a targeted region correlated with varying levels of dysfunctionality in relation to depressive symptoms. rTMS intensity is determined by each patient's resting motor threshold (MT) and adjusted up to a determined percentage of the output, ranging from 80%-120%, delivered at either high-frequency (≤5 Hz) or low-frequency (<5 Hertz) levels of stimulation. Frequency of rTMS refers to the number of pulses per second and number of treatments, while duration includes number pulses per treatment and length of stimulation over time (Bermudes, Lanocha & Janicak, 2017). An additional consideration of spacing effects has emerged as rTMS is delivered over multiple sessions over time (e.g. 1 daily session for 4-6 weeks vs. multiple daily sessions over one week) which may have different effects depending upon more or less spacing between sessions (Goldsworthy, Pitcher & Ridding, 2015). Sometimes referred to as consolidation, these longer-

term effects of rTMS have been shown to occur as a result of time (e.g. 1 hour between sessions) and/or sleep, likely due to combination of stimulation parameters and how these factors effect neuroplasticity protein synthesis and gene transcription. Overall, these specific parameters may vary across rTMS studies creating inconsistencies when assessed in comparison, making these details an important consideration when reproducing and enhancing rTMS effects. Further research should be conducted to address how each parameter impacts treatment outcomes.

**rTMS for Depression**

Repetitive transcranial magnetic stimulation (rTMS) is an established, FDA-approved neuromodulation treatment for individuals with treatment resistant major depressive disorder (MDD) (Kedzior, Gellersen, Brachetti, & Berlim, 2015; O'Reardon et al., 2007). Over the last 30 years, rTMS has developed as a clinical tool and "third pillar" in the treatment of psychiatric disorders while also contributing to advanced methodological approaches by which to further understand associated pathophysiological mechanisms related to behavior, psychopathology and brain functionality (Barker, Jalinous, & Freeston, 1985; Polanía, Nitsche & Ruff, 2018; To, De Ridder, Hart, & Vanneste, 2018). Since FDA approval for MDD and following multi-site, randomized controlled trials, a variety of reviews have been published supporting the clinical use of rTMS for major depression (Gaynes, 2014; Kedzior et al., 2015a; Perera et al., 2016). More recently, some have urged the use of rTMS for less treatment resistant depression (i.e. use for MDD after ≤1 medication trial), after comparing efficacy and lifetime cost of future pharmacologic treatment in this population (Voigt, Carpenter & Leuchter, 2019). Additionally, treatment for other depressive mood related disorders such as bipolar depression, perinatal depression, adolescent depression, and late life-depression has been studied (Fitzgerald et al., 2016; Kazemi et al., 2018; McGirr et al., 2016). Despite evidence of antidepressant efficacy,

further exploration in the variability, optimization and durability (lasting anti-depressant effects or time to relapse) of TMS treatment remain areas of interest as the field continues developing and refining clinical TMS treatment protocols (Janicak & Dokucu, 2010; Weigand et al., 2018).

*rTMS for Bipolar Depression*

rTMS treatment for bipolar TRD typically follows the same guidelines as unipolar TRD, but with additional protocol considerations and safety concerns specific to each patient's history. In open label trials, rTMS for BD has included standard high-frequency LDLPFC, low-frequency RDLPFC and sequential bilateral rTMS (low-frequency right-sided DLPFC followed by high-frequency left-sided DLPFC stimulation), which have shown mixed results and possible treatment induced mania (Fitzgerald et al., 2016; Kazemi et al., 2018; McGirr et al., 2016). With the potential risk for mania/hypomania induction in antidepressant treatment for bipolar TRD, a similar concern for safety and ideal protocol for bipolar TRD with rTMS remains. With these concerns in mind, studies have noted varying levels from absent to low-risk for emergent mania/hypomania during rTMS treatment (Rachid, 2017; Tavares et al., 2017). Other findings warranting further investigation show possible early response in patients with bipolar I and II TRD as compared with unipolar TRD and a primary side effect of agitation leading to potential discontinuation within this population receiving rTMS (Aaronson & Daddario, 2016). However, a recent analysis comparing unipolar and bipolar TRD response trends showed at least comparable antidepressant response between groups and no treatment emergent mania (Phillips, Burr & Dunner, 2019). Overall, more research is needed to support the safest and most effective way in which to utilize rTMS in the treatment and management of bipolar disorder along with recommendations of mood stabilizing medications and adjunct therapies.

## History of rTMS for Mood Disorders

### *Preliminary rTMS Trials*

The initial indication for rTMS in mood disorders began with case reports, case series and small-scale, open-labeled trials. Testing the hypothesis of evidence supporting the correlation between depression and hypofunction in the left prefrontal cortex, George and colleagues (1995) developed an rTMS protocol targeting this region of the brain among 6 "highly medication-resistant depression inpatients," in which two showed significant improvement in mood and one reached remission. Basic comparisons between baseline and post-treatment were reported with two-tailed paired t-tests. Without a clear sense of ideal parameters for rTMS treatment, George and colleagues (1997) conducted a placebo-controlled crossover trial treating 12 depressed patients in random order for two-weeks of either active (20Hz at 80% of MT) or sham treatment, showing a significant improvement in mood after treatment as indicated by the 21-item Hamilton Depression Rating Scale. Additionally, "sham" treatment at this time was a displaced treatment location at a 45-degree angle from the skull. The methodological analysis utilized repeated measures analysis of variance (ANOVA) with order as a between-subjects term and treatment (sham vs. active) and time (week one and week two) as within subject factors.

### *rTMS Clinical Trial Efficacy Methods*

Upon the emergence of literature supporting rTMS as a possible treatment modality for major depression, larger sham-controlled trials emerged to further gather larger samples for efficacy and safety of rTMS. rTMS gained FDA approval after a large, double-blind, multisite (N=23) randomized sham-controlled trial of rTMS in over 300 patients with major depression (O'Reardon et al., 2007). At the time of this trial, prior studies had demonstrated some efficacy;

however, rTMS protocol duration, intensity and durability were widely unknown. Using a sample size requiring 90% power and effect size of .40, this study applied 5 sessions per week at 120% of MT, totaling 300 pulses per session. Primary and secondary depression outcome data were analyzed using analysis of covariance (ANCOVA) and random effects adjustment for site differences. O'Reardon and colleagues (2007) also discussed the issue of rTMS sham (placebo) methodology involving a similarly structured and operated device, prioritizing the best possible way to translate a similar experience related to procedure, sound and sensation.

Completion of the FDA-registration study then led to an extension trial where patients were able to participate in a blinded, open-label trial reporting increasing response and remission rates as rTMS treatment continued, and the same data analysis plan (Avery et al., 2008). After FDA-approval, Optimization of TMS for Depression (OPT-TMS) was sponsored by the National Institute of Mental Health (NIMH) to improve methodologies based on the gaps found in the original trials (George et al., 2010). This included MRI modification for treatment location determination, clinical determination of treatment duration and an improvement in sham conditions as previously mentioned. Logistic regression and control for treatment site, treatment resistance, demographics and duration of episode were use in an intent-to-treat sample of 240 based on an 80% power analysis.

In 2013, the Deep rTMS (dTMS) device was developed utilizing an H-shaped coil shown to penetrate up to 6 cm into the brain, with the ability to activate deeper areas beyond the cerebral cortex (Bersani et al., 2013). The double-blind, sham controlled, multi-site randomized trial of dTMS was similarly structured to the previous rTMS trials with the methodological improvements included allowing for 5 daily sessions per week over the course of 4 weeks with continuation treatment up to 12 additional weeks (Levkovitz et al., 2015).

Randomizing patients into these large-scale, double-blinded, multi-site sham-controlled studies is ideal, though with its own limitations. Due to the nature of the severely depressed population participating in these studies, a multisite approach was required, but controlled for in all studies. Double-blinding patients and providers to treatment vs sham conditions was also employed; however, it is possible that providers experienced with brain region functionality or differences in coils were able to ascertain sham vs control, or patients may have experienced contamination by interacting with those in the other study condition. Overall, since FDA-approval and registry studies were initially conducted, the advancement in more controlled and methodologically sound designs have been employed, and continue to develop (Perera et al., 2016).

*rTMS Naturalistic Observational Studies*

Due to the increase in clinical application of rTMS since FDA-approval and lack of funding for larger-scale, double-blind sham-controlled studies, the bulk of recent and proposed studies have employed naturalistic observation supporting the safety, efficacy, durability and protocol development of rTMS in mood disorders. For example, Carpenter et al. (2012) assessed over 300 patients across 42 rTMS treatment sites in the U.S. while assessing treatment outcomes at baseline and at time-points throughout treatment extending to 6 weeks. Data was analyzed in a last observation carried forward (LOCF) method with more comprehensive approaches including Student's *t*-tests for covariates, ANCOVA to assess change from baseline in repeated measure scores, chi-square analysis for categorical data, survival estimates, ANOVA to assess moderator variables and the analysis of whether psychiatric provider variances of treatment duration differences made an impact. This naturalistic study showed results similar to prior research studies and thus began the continuation of this method in much of current rTMS research. Other

naturalistic observational studies with similar methodological approaches have assessed rTMS durability, quality of life, of antidepressant response various rTMS protocols including high vs low-frequency stimulation and utility of psychotherapy during rTMS (Donse, Padberg, Sack, Rush & Arns, 2017; Dunner et al., 2014; Janicak et al., 2013).

The ability to utilize patient populations in real-world settings allows naturalistic observation to provide insight related to the complex conditions and profiles of individuals including co-morbidities and adjunct medications that are the reality of rTMS patients in clinical settings. However, issues intrinsic to naturalistic settings are the impact on Type II error related to the potential for confounding variables impacting treatment outcomes and the absence of a control group for comparison. In addition, because of the complex comorbidities across rTMS patients experiencing treatment resistant depression, real-life, naturalistic studies lend much insight into the use of rTMS as an advancing clinical tool.

*Meta-analyses & Systematic Review of rTMS for MDD*

Since the variety of rTMS studies has expanded in the past decade, numerous meta-analyses have condensed findings to reveal consistent patterns in overall effectiveness of rTMS treatment for depression and other mood disorders across treatment modalities, with emerging data as to rTMS treatment durability (Brunoni et al., 2017; Kedzior et al., 2015a; Kedzior, Reitz, Azorina & Loo, 2015). Additionally, consensus review recommendations for the clinical applications of rTMS in the treatment of depression are regularly updated. McClintock and colleagues (2018) reviewed the most recent recommendations and overview of evidence for rTMS including recommendations on maintenance rTMS post anti-depressant response. Of particular relevance to this study, the current consensus reported that exposure to newer rTMS paradigms such as iTBS and “accelerated” dosing, generally appears to be safe. With respect to

maintenance treatment recommendations, it is acknowledged that a maintenance plan must be in place to prolong the "improved clinical state" achieved by rTMS; however, the limited number of controlled trials exploring durability and maintenance make this a difficult question to answer. At present, they were unable to recommend 1 strategy, but instead deferred to evidence-based approaches such as repeating rTMS, utilizing antidepressant supplementation, and augmenting rTMS with other psychotherapeutic or physical interventions (e.g. exercise).

*rTMS Retrospective Reviews*

Retrospective reviews have become a way for rTMS clinicians to review readily available patient data, typically collected at TMS consultation, time points throughout treatment and at follow-up. This method is a cost-effective and easily attainable way to utilize clinical data while answering questions address gaps in the literature, among patients treated in naturalistic settings. For example, Schulze and colleagues (2017) utilized 130 patient charts to assess whether an increase in number of pulses or number of sessions would impact therapeutic effect. In doing so, they were able to add to the literature supporting the safety and tolerance of an increased number of daily pulses while also ascertaining therapeutic gain in their sample as being associated with number of sessions and not pulses. Additionally, studies such as Rostami et al. (2017) show a differing methodology used in retrospective, naturalistic studies utilizing clinical trial data to shed light on clinical predictors via Mutual Information (MI), Kullback-Leibler divergence (KLU) and receiver operating characteristics when compared to depression measures and demographic characteristics.

Despite the lack of power, control over fidelity, and potential confounding variables inherent in retrospective data analysis, the ability to take previously obtained patient data and systematically assess unanswered questions in a difficult to treat population undergoing a widely

unknown treatment method may be of great utility. In addition to adding to this body of literature, retrospective chart reviews certainly have their place in being able to guide future double-blind, randomized clinical trials.

*Accelerated rTMS*

A standard course of rTMS treatment based on seminal studies and continued trial structures includes daily treatment (20-40 minutes) over the course 4-6 weeks. In addition to the potential risk for suicide in severely depressed populations, the consumption of time and resources to accommodate such a treatment structure has employed a sense of urgency in developing an accelerated rTMS paradigm while continuing to explore parameters that will also produce more robust antidepressant efficacy (Sonmez et al., 2018). rTMS clinicians and researchers have attempted to accelerate protocols with mixed results, possibly due to the variation of rTMS protocols across studies. A recent retrospective review of standard rTMS delivered twice daily (with 15-minute inter-session intervals) as opposed to once daily sessions, showed a greater decrease in symptom severity over a shorter period of time (Modirrousta, Meek, & Wikstrom, 2018). Additional studies have shown added benefit from increased "sessions" or pulses, but others show this may not have the same additive effect without thoughtfully structured inter-session intervals (Baeken et al., 2019; Schulze et al., 2017; Williams et al., 2018)

*Intermittent Theta Burst Stimulation*

Intermittent theta-burst stimulation (iTBS) is a safe and novel form of patterned, excitatory and inhibitory rTMS which has shown robust antidepressant response in treatment resistant depression populations (Berlim et al., 2017; Chung, Hoy & Fitzgerald, 2015; Huang et al., 2005; Li et al., 2014; Oberman, Edwards, Eldaief, & Pascual-Leone, 2011; Rachid, 2017).

Demonstrated by motor cortex excitability and theorized to increase calcium ion concentration, iTBS is differentiated from standard rTMS by inducing a more robust response to long-term potentiation (LTP) of neural plasticity through both high and low-frequency, patterned stimulation (see image below for stimulation differences) (Huang et al., 2005).
Compared to standard 10 Hz rTMS treatment over the LDLPFC, iTBS has recently been deemed "non-inferior" with potential benefit in expediting response with a shorter treatment time and fewer treatment sessions required (Bakken et al., 2015; Blumberger et al., 2018). In August of 2018, the US FDA approved the 3-minute iTBS protocol for MDD based on Blumberger's (2018) double-blind, randomized control trial. Additionally, iTBS has shown the potential for more durable anti-depressant effects compared with standard rTMS (Di Lazzaro et al., 2011; Huang et al., 2011).

By safely employing more pulses over the shorter course of 1-2 weeks, accelerated iTBS (aiTBS) has shown potential in the management of acute, treatment resistant depression (TRD) (Cole et al., 2019; Desmyter et al., 2016; Duprat et al., 2016). Additionally, there is evidence that aiTBS may significantly decrease suicide risk for up to one-month post-intervention (Desmyter et al., 2016). However, longitudinal anti-depressant durability and specific symptom response optimization have not been examined in studies of aiTBS treatment outcomes.

*rTMS Durability*

Despite the most promising response and remission rates of any treatment, if durability is lacking, so is the effective use of the treatment, overall. As rTMS has continued to develop in recent years, few studies address long-term antidepressant durability and sustained antidepressant response to treatment, which may inform treatment re-introduction, continuation or other approaches in maintaining effects and preventing symptom relapse. Similar to any other

therapeutic intervention, there must be consideration of variable effects and long-term treatment maintenance. Differing approaches toward managing rTMS antidepressant effects range from acute series re-introduction upon symptom worsening, to less-frequent, spaced rTMS sessions (e.g. weekly or monthly) thought to help maintain effects after an acute response. In a recent review, Senova and colleagues (2018) included 19 studies from 2002 to 2018 assessing rTMS responders after an acute series of rTMS. In this review, a meta-analysis of 732 patients across 18 studies showed approximately 66.5% response at 3-months, 52.9% at 6-months and 46.3 at 1-year post-treatment. Heterogeneity was low to moderate for all time-periods, across these studies. Predictors of durability in these studies included female sex and maintenance treatment; however, the studies included in this review utilized different rTMS parameters and lacked structure in maintenance planning. Some studies utilized a scheduled maintenance plan, while others used clinical scales to initiate maintenance upon re-emergent depressive symptoms.

Of particular relevance to this study is the durability of accelerated and iTBS specific durability, which are lacking beyond short-term follow-up periods. Holtzheimer et al. (2010) reported on an accelerated, 2-day, 15 total rTMS session protocol resulting in similar but less robust antidepressant response durability (immediate post-43%, 3-weeks post-36% and 6-weeks post-36%) compared to standard rTMS. Other accelerated protocols have since tested efficacy of other accelerated paradigms (e.g. 20 aiTBS sessions over 4 days) and have not yet reached questions of durability beyond 1-2 months; however, highly suicidal TRD populations held a significant decrease in suicide risk over these follow-up periods (Desmyter et al., 2016). The recent non-inferiority iTBS trial showed similar trends of response up to 12 weeks post-treatment in both iTBS and rTMS groups, but exact rates are not clear (Blumberger et al., 2018). Overall,

aTMS and iTBS studies may have comparable durability profiles; however, this literature is scarce and should be explored in future trials.

*rTMS Predictors of Relapse*

Due to variable rates of antidepressant response (≥50% decrease in depression scores) and remission (virtually asymptomatic response to treatment based on specific depression scale cutoff, e.g. HDRS-6 of ≤4) across rTMS studies for TRD, predictors of response and relapse have been assessed in numerous rTMS studies and reviews. Miljevic et al. (2019) recently evaluated potential predictors of relapse in a systematic review across rTMS studies following participants after an acute series of rTMS treatment. In sum, variables associated with shorter time to relapse were found to be comorbid anxiety, fewer total rTMS sessions and longer time to antidepressant response, male sex, depressive episode duration and residual symptomology. Comparable to prior ECT literature, the use of maintenance rTMS has shown to predictor longer antidepressant durability; however, other studies have shown no group differences in durability among those receiving maintenance rTMS vs those who do not (Miljevik et al., 2019; Senova et al., 2018). Overall, these reviews may provide an indication as to where predictors of rTMS antidepressant durability for TRD may lie; however, due to the limited studies available including a range in protocol variation and lack of reproduction in other studies, these data must be further explored in order to support any conclusions.

*rTMS Measures*

As the FDA-approved indication of rTMS covers treatment resistant major depression, primary and secondary measurement tools utilized remain empirically validated depression scales. Additional measures assessing safety, quality of life, disability and other mood related

symptoms have been utilized. Advanced methods such as electroencephalography (EEG) and magnetic resonance imaging (MRI) have more recently been applied.

*Safety Measures*

Safety is typically assessed via number of adverse or spontaneous events experienced during rTMS treatment (e.g. seizure, pain at the site of the scalp, facial muscle contractions) and over the course of treatment (e.g. headaches, fatigue, suicidality). All rTMS studies report side effects or adverse events, typically in the fashion that they are reported from patients to rTMS treatment providers and without a specific measurement tool (Levkovitz et al., 2015).

*Psychiatric Measures*

The FDA-approval study, among others utilized the Montgomery–Asberg Depression Rating Scale (MADRS) as the primary depression measure, and secondary outcomes included changes on the 17 and 24-item Hamilton Depression Rating Scale (HAM-D) and response/remission rates with both scales (Levkovitz et al., 2015; O'Reardon et al., 2007). Many studies also utilize Clinical Global Impression Severity of Illness and the Inventory of Depressive Symptoms-Self Report (IDS), Beck Depression Inventory (BDI-II) and Quick Inventory of Depressive Symptoms (QIDS) (George et al., 2010; Janicak et al., 2013; Schultze et al., 2017; Taylor et al., 2017). Consistent but strategic use of clinical outcome measurement tools (e.g. depression scales) in the assessment of rTMS remains an important topic of discussion as providers differ in opinion as to what best captures patient response to rTMS. Additionally, this issue remains important point of contention as it guides treatment and many times, healthcare coverage for patient insurance companies. Despite the differing use in depression measurement tools for rTMS outcomes, future rTMS methods should carefully assess and justify their decision for selecting such scales.

*Other Psychiatric Measures*

Due to the increased risk for treatment induced mania, some studies assessing rTMS in the treatment of bipolar depression have utilized the Young Mania Rating Scale (YMRS), whereas others clinically probe with questioning and patient observation to account for any changes indicating mania/hypomania (Fitzgerald et al., 2016). Other measurement tools are less frequently used in rTMS studies including the Patient Global Impressions Improvement Scale (PGI-I), Quality of Life Scales, Sheehan Disability Scale and the Depression, Anxiety and Stress Scale (Donse, Padberg, Sack, Rush & Arns, 2017; O'Reardon et al., 2007).

*Neurophysiological and Imaging Methods*

Advances in neurophysiological methods have grown immensely in the past decade. Earlier rTMS studies utilizing positron emission tomography (PET) are not feasible for longer-term TMS studies as ionizing radiotracers are unsafe for repetitive participant exposure. In recent years, advanced methods such as electroencephalography (EEG) and magnetic resonance imaging (MRI) paired with rTMS have allowed for more in-depth exploration of short- and long-term effects of rTMS as well as more global or downstream neural effects of pulse propagation. As animal model research has emerged to support translation into human studies, fMRI has been utilized to further probe functional connectivity and mechanism of action in relation to TMS stimulation (Seewoo et al., 2018; Vink et al., 2018). On the other hand, EEG will allow for further exploration in brain wave activity and more specifically, the ability to assess the synchronization or "phase-lock" of rTMS pulses with neural oscillations. Another approach toward enhancing the ability to accurately engage specific treatment targets with rTMS, is the use of E-Field modeling (Bikson et al., 2018). With the generation of electrical fields via magnetic induction, models are being developed to optimize spatial

stimulation patterns based on a variety of potentially generalized algorithms in order to produce the most individualized, realistic simulations for rTMS treatment targeting (Saturnino et al., 2019). Although many of these advancements are in their infancy, it is important to consider the most appropriate and feasible method.

*Biomarkers*

Biomarkers are objective and observed "signs" or indications of medical state that can be measured and reproduced, accurately (Strimbu & Tavel, 2010). In recent years, an emerging body of literature has developed assessing the potential landscape of biomarkers ranging from genomics, proteomics, metabolomics and lipidomics, to functional and structural neuroimaging, electrocephalography (EEG) and heart rate variability (HRV) biomarkers in the context of neuropsychiatric disorder diagnosis, prognosis and treatment outcome response (Loo et al., 2016; Lozupone et al., 2012; Quinones & Kaddurah-Daouk, 2009). For example, low frequency heart rate variability (lf-HRV), measured by beat to beat interval, has shown to be a "trait-marker" of major depressive disorder, with an increase in measured HRV associated with a reduction in depressive symptoms across this population (Beauchaine & Thayer, 2015; Brunoni et al., 2013). Similar HRV measures have been added to the double-blind, placebo controlled RCT assessing the SAINT protocol, while also being assessed at post-SAINT follow-up time-points. Herein may also lie the potential capacity to predict relapse with a method such as HRV, during post-rTMS follow-up time-points. Identifying biomarkers will only continue to grow as a way to more objectively measure physiological correlates of depression and in turn, how treatment may be approached.

*aiTBS Theoretical Framework*

In the 2014 revision of clinical trial requirements supporting a "precision medicine" approach, the National Institutes of Health (NIH) began transitioning into the requirement of a neural "target or mediator of the intervention being tested" to evaluate both the clinical effects of the intervention and the mechanistic components of the disorder, pathology, or targeted outcome being explored (Bikson et al., 2018). As the inter-individual variation in TMS response continues to be assessed across TMS treatment paradigms, studies have prioritized the exploration of individualized treatment target *location* and *dosage,* which may be key factors in improving treatment response (Fox et al., 2012; Johnson et al., 2013; Yip, George, Tendler, Roth, Zangen, & Carpenter, 2017). An additional consideration in applying any rTMS paradigm is how the effects of timing consecutive sessions impacts neuroplastic effects and in turn, treatment outcomes. Therefore, this was considered as a part of the protocol development related to spacing between treatment sessions in the parent study (Cole et al., 2019).

*Accelerated iTBS paradigm*

As paradigms in rTMS across clinical applications have emerged, accelerated iTBS has received little exploration thus far, with primary focus on safety, and reduction in suicidality and depression among TRD patients (Cole et al., 2019; Desmyter et al., 2016; Duprat et al. 2016). With shorter treatment sessions showing equal efficacy, iTBS has been approached as a way to more quickly and effectively target symptoms over a condensed period of time. For example, Desmyter, Duprat and colleagues (2016) found 20 sessions of LDLPFC aiTBS over 4 days to be safe and effective in reducing symptoms of depression and suicidality; however, the sham group also experienced a significant reduction in depressive symptoms. The first to report utilizing up to 50 iTBS sessions over the course of 5 days includes the data in this study as

preliminarily reviewed by Williams (2018) and recently published in its entirety in the parent study (Cole et al., 2019). Following an inpatient introduction to accelerated iTBS, this paradigm was extended to an open label group of participants who safely received 5 days of 10 daily sessions for a total of 50 sessions and 90,000 pulses. No participants experienced cognitive worsening, manic/hypomanic conversion or adverse events. Any additional retreatment sessions followed the same protocol.

*Spaced Learning Theory*

As a core concept of learning, memory, and recovery from neurological damage, "neuroplasticity" has been established as the brain's ability to change and recover its connectivity throughout the lifespan. For many types of learning, spaced training vs. consolidated or mass training results in greater memory formation. Spaced training or spaced learning (used interchangeably) incorporates long intervals between training sessions, whereas mass training consolidates training with shorter time intervals between periods of training sessions. In recent years, research has started to translate the potential optimization of effects seen in spaced learning shown via engagement in learned motor skills, lists, facts and concepts, and educational knowledge training, over a variety of time periods (e.g. seconds, minutes, hours, days, etc.), to the molecular and synaptic effects observed in neuromodulation (Smolen et al., 2016). Through inductive change, brain stimulation has found to produce neuroplastic effects resulting in LTP and long-term depression (LTD) (Goldsworthy et al., 2015). Goldsworthy (2015) additionally discusses the assumptions of cumulative effects upon utilizing "once-daily" NIBS models without a stronger consideration of inter-session timing effects. While assessing ideal intervals between theta-burst stimulation intended to maximally increase LTP, Lynch and colleagues (2013) found an interval of 40–60 minutes between stimulation sessions is needed for

sequential theta-burst to further increase LTP (Kramár et al., 2012). Due to the LTP-like optimization during the 40-60-minute interval, the SAINT protocol utilized this time frame for inter-session intervals in an attempt to achieve the most durable effects.

**rTMS ROI Target**

*Target Identification*

Generally targeting the dorsolateral prefrontal cortex (DLPFC) with TMS in the clinical treatment of depression has been a standard parameter, as the seminal, efficacy trials of rTMS identified this region based on positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging showing a pathophysiological link in addition to brain lesion and mood dysregulation association found in the DLPFC (Drevets et al., 2008; Mayberg, 2009; O'Reardon, 2007). However, due to a lack of understanding regarding the mechanistic antidepressant effects of rTMS, the variation in treatment targeting and the more recent ability to utilize advances in neuroimaging, resting-state functional connectivity has been employed to more precisely target the ROI while also allowing for biomarkers in potentially identifying associations with treatment outcomes (Gratton et al., 2013; Iwabuchi et al., 2017; Philip, et al., 2018; Weigand et al., 2018). To identify the treatment target in the parent study, an intrinsically anti-correlated DLPFC-SCC treatment target approach was utilized (Fox et al., 2012) to identify the ROI for targeting. The corresponding scans used to target the treatment location were also used as a way to measure pre-post and 1-month follow-up changes in this brain region. To answer questions related to both clinical and mechanistic effects, these data are being analyzed and will be assessed in association with these durability results. After using the innovative combination of ROI targeting with RFC guiding the neuro-navigated treatment target as a predictor of dose response while also confirming the targeted location with E-field modeling, we

may be able to glean future insights as to how these important brain regions functionally change as a result of the SAINT protocol and what additional changes occur post-stimulation in relation to other behavioral and physiological outcomes.

**Summary**

In summary, decades of research in depression, and more specifically TRD populations, have advanced to a turning point in the state of translational psychiatry. Encompassing a more interdisciplinary approach toward building and refining novel treatment modalities for these populations, rTMS is an example of many fields coming together to better understand and create new approaches in depression treatment methodology. Relevant to the parent study is the use of novel, translational, neuropsychiatric science as it combines advanced methods in 1) accelerated dosing and treatment delivery, 2) brain region of interest targeting and 3) spaced iTBS dosing. The current study fills an additional gap where durability and retreatment literature are lacking, and predictors of response are inconsistently reported. Additionally, by further assessing baseline depression vs. treatment refractoriness (MSM), clarification may be obtained as to whether a different approach may improve the most optimal rTMS treatment outcomes, with the greatest chance for a longer, more durable antidepressant response. Finally, this study will add to the current state of the science in describing how future rTMS studies may assess factors related to durability in a small, open label pilot study, and what implications this may have for the future in rTMS treatment and research.

# Chapter 3: Methods

The primary aim of this study was to examine up to 6 months of aiTBS antidepressant response durability (or, time to relapse) among prior rTMS non-responders and rTMS naïve individuals with TRD, using clinician-rated depression measures, at post-treatment time-points. Secondary aims focused on the use of day to response during the 5-day treatment period, baseline depression severity, and baseline treatment refractoriness as potential covariates and predictors of response. An additional aim was to assess anti-depressant durability among the group of participants who responded (n=31) or partially responded (n=1) to SAINT and were retreated with the same, 5-day treatment protocol (see Figure 1 for SAINT Study Timeline with Follow-Up Time-points and Figure 2 for Participant Study Flow Diagram).

## *Study Design*

This study involved a secondary data analysis of existing data from 33 participant records kept in a secure online data storage capture tool. The parent study involved review of the feasibility, tolerability and preliminary efficacy of an accelerated, high-dose, resting state functional connectivity MRI (fcMRI)-guided iTBS protocol for treatment resistant depression (Cole et al., 2019). This protocol yielded response and remission rates of approximately 90%, showing aiTBS to be a safe and feasible 5-day treatment for TRD. All 31 participants referenced in the parent study are included in this study sample, with an additional 2 participants who were treated after the submission of the parent study and have not received retreatment. Demographic and clinical data were extracted from patient forms or entered by clinicians or research assistants over the course of this study after being de-identified using alphanumeric coding and stored and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at Stanford University (Harris et al., 2009). REDCap is a secure, web-based application

designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

*Sample*

This study included data from 33 participants who were recruited by the Stanford Brain Stimulation Lab under NIH Study NCT03240692, approved by the Institutional Review Board (IRB) at Stanford (Study PI: Nolan Williams, MD). The IRB approval for this study was deferred to the Stanford IRB by the University of Washington external IRB prior to study implementation. Inclusion criteria for the parent study were: individuals aged 18 to 80 with a primary diagnosis of major depressive disorder in a current major depressive episode or bipolar II mood disorder in a current major depressive episode. All participants received the Young Mania Rating Scale (YMRS) to detect any treatment emergent mania/hypomania. Diagnoses were confirmed by the study PI or research associate who performed the DSM-5 Structured Clinical Interview for Depression (SCID) or Mini International Neuropsychiatric Interview (MINI). Participants were required to have a minimum score of 21 on the Hamilton Depression Rating Scale (HDRS-17) and no response to at least one antidepressant medication (6-week trial duration minimum). Participants were required to qualify as "Moderate or Severe Treatment Refractory" using the Maudsley staging method, which includes prior treatments, symptom severity and duration of presenting episode (Fekadu, Wooderson, Markopoulou & Cleare, 2009). Participants continued their antidepressant regimen but were required to stabilize for 6 weeks prior to enrollment in the study. Participants opting to continue antidepressant medications were required to maintain only the selective serotonin reuptake inhibitor (SSRI)

class medications. (Participants on a different class of antidepressant were switched to an SSRI and stabilized.) Participants were asked to continue the same antidepressant regimen throughout the study. Exclusion criteria of the parent study consisted of any neurological condition, history of a psychotic disorder, substance abuse disorder, major systemic illness, current mania, obsessive compulsive disorder (OCD), history of epilepsy or any TMS or MRI contraindications. All participants agreed to be assigned to and followed by a psychiatrist throughout the study, if they did not already have one.

**Parent Study Review**

*Recruitment and Screening*

Participants included in the parent study were recruited through the Stanford psychiatry outpatient clinic including a database for potential research subjects who previously consented to research contact through the clinic and via physician referral. Additionally, printed flyers and the Stanford Research Registry (protocol 25422) of approximately 1,000 potential research subjects were used to recruit participants for screening. Participants were screened over the phone for inclusion/exclusion criteria and TMS (see Scanning and TMS Safety Questionnaire-Appendix D) safety screening, MRI safety screening, and medical and psychiatric history. Participants who met criteria were seen in the depression research clinic for a consultation. During this consultation, potential participants were informed of standard of care treatments as well as the protocol involved in this study. Neuropsychiatric history and baseline measures were collected at that point and repeated, depending on the time prior to starting treatment due to scheduling conflicts. All participants completed informed consent upon moving forward with the active portion of the study.

*Functional Magnetic Resonance Imaging (fMRI)*

All participants received a resting state fMRI scan approximately 2 days prior to their aiTBS treatment course. These MRI scans were used to identify the most anti-correlated ROI between the LDLPFC and SCC (Fox et al., 2012). A specific algorithm adapted in Flywheel, Stanford's imaging data capture and computational analysis tool, was utilized to identify the cluster with the greatest anti-correlation between the LDLPFC and SCC. This anti-correlation cluster was then used to create the individualized target for each participant's aiTBS coil placement. The 3T GE Discovery MR750 scanner with 32-channel imaging coil was used to acquire scans at the Stanford Center for Cognitive and Neurobiological Imaging.

*E-field Modeling*

In the parent study, E-Field modeling was utilized to confirm the likelihood that the target engagement of the DLPFC and SCC was accurate based on the positioning used in this study, (Bikson et al., 2018). Simulation of Non-Invasive Brain Stimulation (SimNIBS) is an open-source pipeline for simulating electric fields that was used to analyze TMS spatial distribution of the stimulation effects on the brain via the pre-TMS T1-weighted structural MR images while also generating a 3-D mesh modeling of each brain (Saturnino, Antunes, Stelzer & Thielscher, 2015). SIMNIBS software was then used to perform iterative E-field modeling to confirm target engagement. Additionally, a MagVenture AP coil file was used to record its position in space including handle orientation, which signifies the magnetic field direction. This was not a part of the durability analysis in the present study, but a part of the initial methodological procedures.

*aiTBS Treatment*

Treatment dosage was determined in a preliminary mapping session during the first aiTBS session and delivered at 90% of resting motor threshold. Individualized LDLPFC functional location was determined via Localite Neuronavigation System (Stokes et al., 2005). In the initial treatment session, each participant's resting motor threshold (RMT) was determined using single pulse TMS over the motor cortex. RMT was defined by eliciting a visible contraction of the right first dorsal interosseous or abductor pollicis brevis muscle in 50% of 10 trials at the lowest power setting needed. RMT was re-checked prior to each active, daily treatment session for each participant. Participants then received five days of ten times daily active aiTBS over the anti-correlated functional connectivity region (DLPFC and SCC) targeted by baseline fMRI imaging. Treatment was delivered using the Magstim device (Magstim Company Ltd., Whitland, UK). aiTBS sessions were scheduled in a 5-day sequence (typically Monday-Friday), for a total of 50 sessions, with a 50-minute interval between consecutive sessions.

Treatment parameters followed Li and colleagues (2014) protocol: 3-pulse, 50Hz bursts with 2-second pulse durations (trains), and 10-second inter-train intervals, for a total of 1800 pulses per session. This separation between stimulations decreases the risk of associated TMS side effects (e.g. scalp discomfort at the site of treatment, headache). Fifty-minute intervals between sessions was modelled after animal studies showing optimization of one-hour intervals in producing long-term potentiation (LTP), thought to increase synaptic strength following high-frequency iTBS stimulation (Li et al., 2014; Lynch et al., 2013;). During breaks, participants were able to participate in iPad or audio based cognitive behavioral therapy activities or mindfulness content and may also have been asked to rate their enjoyment of this content on a scale from 1-10 with 1 being no enjoyment to 10 being the greatest level of enjoyment.

*Follow-up Time-Period* (see Figure 1 for Study Timeline including follow-up time-period):

Participants completed Zoom call visits at weeks 1 ,2, 4, 6 and 8 after the final treatment stimulation session. A trained rater performed the Hamilton Depression Rating Scale (HDRS-6), Montgomery-Asberg Depression Rating Scale (MADRS), as well as self-reported medication reviews. Following this period, HDRS-6 was administered every two weeks (by Zoom) for up 6 months. For participants who experienced symptom worsening (i.e. ≥25% increase in depressive symptom scores from baseline) after responding or remitting to the first aiTBS treatment series, a second acute series of aiTBS treatment was proposed and if accepted, re-introduced. For participants who did not have an anti-depressant response to aiTBS treatment, contact with the primary psychiatric provider was made to discuss further treatment recommendations and a plan to return to their care.

***Measures***

*Demographics*

Demographic data including medical and psychiatric history (e.g. prior hospitalizations, medication history and current medications, prior TMS and ECT history, etc.) was collected and recorded in a standard, psychiatric interview at rTMS screening including data from the SCID & MINI during the parent study. Data were then input and stored in REDCap and made available for secondary data analysis extraction for this study. Primary demographic variables used in this study were age, age of depression onset, illness duration, sex, prior rTMS, prior rTMS non-response, prior ECT and prior ECT non-response and diagnoses.

*Clinical Covariates*

Depression Treatment Refractoriness

The Maudsley staging method (MSM) (Appendix A) was used in the parent study to assess overall treatment refractoriness including prior treatments, severity of depressive episode and duration of episode (Fekadu et al., 2009). The MSM differs from treatment severity in that it encompasses 5 factors found to impact level of depression treatment resistance (e.g. current depressive episode duration, number of failed medication trials, augmentation of medications used, ECT used, and baseline depression severity). The scoring convention for the MSM allows for a range of 0-15, with severity score categories suggested as: mild (3-6), moderate (7-10), and Severe (11-15) (Fekadu, Donocik & Cleare, 2018). The MSM has shown to have validated predictive validity in longer-term course illness, depressive episode persistence, and functional impairment. The MSM (Fekadu, Donocik & Cleare, 2018) has "independently predicted (1) being in an episode for 50% or longer of the follow-up duration (OR = 2.11, 95% CI = 1.25 to 3.57), (2) being in an episode at the time of follow-up assessment (OR = 1.89, 95% CI = 1.17 to 3.05), (3) being persistently in an episode throughout the follow-up period (OR = 2.01, 95% CI = 1.14 to 3.54), and (4) total months spent in a depressive episode (OR = 1.22, 95% CI = 1.06 to 1.40)." In the present study, the MSM was used as a continuous covariate to assess whether treatment refractoriness was associated with post-SAINT antidepressant durability. Participants in this study ranged from moderate to severe (7-15) levels of treatment refractoriness on the MSM.

**Depression Baseline and Outcome Measures**

Two primary outcome measures (HDRS-6 and MADRS) were used to assess baseline depression severity and durability at post-aiTBS time-points, as detailed below. The MADRS was used as a second co-variate to assess whether baseline depression severity (categorical or continuous) was predictive of post-SAINT anti-depressant durability.

*Day of Response*

Response (≥50% reduction in depression scores) occurring on one of the 5 days of SAINT was used as a third, categorical covariate to assess whether there was an association between day of response and post-SAINT anti-depressant durability.

*Depression Scales*

The Hamilton Depression Rating Scale (HDRS-6) was the primary measure used to assess depression changes from baseline, over the course of the acute 5 days of treatment, immediate post-treatment, and post-treatment at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24. The HDRS-6 is a six-item clinician rated measure comprised of symptoms targeting depressed mood, feelings of guilt, work and activities, retardation, and somatic symptoms. The reliability, replicability and sensitivity of the HDRS-6 has been deemed comparable to the longer HDRS-17, 21 and 24 item versions (Hamilton, 1960; O'Sullivan, Fava, Agustin, Baer, & Rosenbaum, 1997; Trajković et al., 2011). The HDRS-6 cutoff used for "remission," is defined as a total score of ≤ 4. The HDRS-17 was also used to assess immediate-post, and post-treatment time-point weeks 1, 2, 4, 6, 8; however, this scale was limited to descriptive comparison data for the purpose of this study (see Appendix B for the full scale).

The Montgomery-Asberg Depression Rating Scale (MADRS) is a 10-item, clinician-rated diagnostic scale with an overall score ranging from 0 to 60 based on 6-point scale responses; higher scores indicate higher depression severity. The MADRS was administered at baseline, immediate post, and at post SAINT time-point weeks 1, 2, 4, 6, and 8. The typical cut-off points are normal (0-6), mild depression (7-19), moderate depression (20-34) and severe depression (>34); however, the MADRS was used primarily as a continuous predictor of response (Herrmann, Black, Lawrence, Szekely & Szalai,1998; Müller-Thomsen, Arlt, Mann,

Maß, & Ganzer, 2005). The MADRS is designed to be particularly sensitive to anti-depressant treatment effects and includes items related to observable and patient-reported symptoms of sadness, inner tension, sleep, appetite, concentration, lassitude, anhedonia, pessimistic thoughts and suicidality. Individual items and overall scores from the MADRS were utilized to assess anti-depressant treatment response and potential predicting factors. (Montgomery & Asberg, 1979). The MADRS was used as a primary outcome measure in the parent study as it was found to be more sensitive to changes in depression (Cole et al., 2019). Finally, a cutoff of <10 was used to categorize "remission" (Hawley, Gale & Sivakumaran, 2002). See Appendix C for the full scale.

**Data Analysis**

Participant data were extracted from the Stanford REDCap database designed specifically for the parent, open label study (Cole et al., 2019). SPSS for Windows v25.0 was used for data analyses including basic descriptive statistics (e.g. baseline sample characteristics such as age, sex, marital status, etc.). Descriptive data including sample size, depression score means, and mean depression score change of primary (HDRS-6) and secondary (HDRS-17 & MADRS) depression scales at each post-SAINT follow-up time-point are included in Tables 4 and 5 for both the acute (Table 4) and retreatment (Table 5) groups. Mixed effects multilevel models were used to assess post-treatment changes in treatment means, described in Tables 4 and 5. The longitudinal models account for both individual differences in the average depression level and individual differences in the depression trajectory across the weeks of the study. Differences in change from post-test to follow-up weeks were assessed using Wald $\chi^2$ with significance set at $p \leq .05$.

Data analysis methods are itemized by each aim as follows:

**Aim 1**: Explore and describe the antidepressant durability (time to relapse) after a novel, aiTBS (SAINT) paradigm in a TRD anti-depressant responder group, using the clinician-rated HDRS-6 depression measure at post-treatment weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24, while assessing group differences between prior rTMS non-responders and participants who had not received prior rTMS (rTMS naïve).

Kaplan-Meier survival analyses were used to assess overall time to event, with the "event" as relapse from response (return to ≤ 50% on depression symptom scale) or remission (≤4 HDRS-6 score). Group differences (e.g. prior rTMS non-responder's vs rTMS naïve) were noted as significant at a p-value of ≤ .05 and reported using the Breslow (Generalized Wilcoxon) test.

**Aim 2**: Assess the relationships between durability (time to relapse) and a) time to response/remission (day 1, 2, 3, 4 or 5 of acute aiTBS), b) treatment refractoriness (Maudsley Staging Method) and c) baseline depression severity (using the MADRS, confirming with HDRS-6).

Kaplan-Meier Cox regression analysis was used to assess multiple predictors of survival including categorical and continuous covariates. Univariate cox regression was first used to assess individual clinical covariate predictors of antidepressant durability including 1) baseline depression severity (MADRS) (categorical), 2) day of response (day 1, 2, 3, 4 or 5 during acute treatment) (categorical) and 3) treatment refractoriness (MSM) (continuous). A second series of univariate Cox regression was used to assess individual demographic covariates including age (continuous), sex (categorical), illness duration (continuous), and depressive illness age onset

(continuous). Significant univariate predictors were included in a final multivariate model to assess their collective impact on antidepressant durability.

**Aim 3**: Explore the anti-depressant durability (time to relapse) of a second aiTBS treatment series for those who relapsed during the 6-month period.

Kaplan-Meier survival analyses were again used to assess time to event, with the "event" as relapse from response (return to ≤ 50% on depression symptom scale) or remission (≤4 HDRS-6 score). Group differences (e.g. prior rTMS non-responder's vs rTMS naïve) were noted as significant at a p-value of ≤ .05 and reported using the Breslow (Generalized Wilcoxon) test.

# Chapter 4: Results

An overview of the parent study results reviewing pre/post SAINT response and remission rates, percent change in depression measures and immediate outcomes are detailed in Cole et al. (2019). Due to the addition of 2 participants since the submission of the parent paper manuscript, Cole et al. (2019), response and remission rates are re-calculated below.

## Sample

A total of 33 participants with a current diagnosis of MDD (n=24), Bipolar Disorder Type II disorder (n=4), Bipolar Type I disorder (n=2) or co-morbid Parkinson's Disease (n=3) in a current major depressive episode were included in this study (see Demographics Table 1). Individuals included in the durability data assessed after the acute SAINT phase were limited to the 31 participants who responded/remitted to the acute SAINT protocol (see Figure 2 for SAINT Participant Study Flow Diagram). The two participants excluded in these acute series data analyses were one non-responder and one partial-responder (25-50% decrease in depression score from baseline). The partial-responder was re-treated and included in the retreatment group (n=16). Across all participants, the mean age was 48.7 (SD=16.8), and all except one participant met the Maudsley Staging Method (MSM) criteria for severe treatment refractoriness. Baseline depression severity was severe or very severe across all participants. For additional demographic information on this population, see Cole et al., 2019.

## Primary Outcomes

Response was defined as a ≥50% reduction on the MADRS or HDRS-6 scale, while remission was defined as a score of <10 on the MADRS scale and ≤4 on the HDRS-6 scale on or before the end of treatment day 5. Of participants who experienced symptom worsening (25-50% increase in HDRS-6 depressive symptoms during follow-up from post-treatment scores) or

relapse (≥50% increase in HDRS-6 depressive symptoms during follow-up from post-treatment scores), 16 chose to be retreated, which included the acute-series partial responder. The remaining 16 participants (50%) did not receive retreatment.

Overall, 94% of participants completing the acute-SAINT series were anti-depressant responders at 1-month, with 58% (18) at 3-months, and 13% (4) holding response at 6-months post-SAINT (see Table 2). Of the 16 participants who were not re-treated, 10 (63%) relapsed (≥ 50 increase in HDRS score) during the 6-month post-SAINT time-period, whereas 13 (81%) of participants in the retreatment group relapsed during the 6-month follow-up time-period. Three participants are still being followed in this study (2 participants are at 8- and 22-weeks post-acute series and 1 participant is at 8-weeks post-retreatment series), and all currently meet "responder" and "remitter" criteria. As their data will be shown as "censored" at their most recent time-point in these analyses (see Figures 3 and 4 at weeks 8 and 22 and Figure 5 at week 8), the following durability results are likely an under-estimate of post-SAINT durability.

*Durability findings*

Findings are itemized by aim as follows:

**Aim 1:** Explore and describe the antidepressant durability (time to relapse) after a novel, aiTBS (SAINT) paradigm in a TRD anti-depressant responder group, using the clinician-rated HDRS-6 depression measure at post-treatment weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24, while assessing group differences (i.e. prior rTMS non-responders). It was hypothesized that participants who previously did not respond to a conventional series of 4-6-week rTMS would experience early relapse compared with the rTMS naïve participant group.

Kaplan-Meier survival analysis showed an overall time to *response* relapse (based on ≥50% reduction from baseline HDRS-6 score) estimate of 14.37 weeks (SE=1.84). Previous

rTMS non-responders (n=11), showed fewer weeks of durable antidepressant response [$X^2$=7.69, p=.006, mean 8.46 weeks (SE=2.73)] than those who had not previously experienced rTMS (mean 17.76 weeks, SE=2.11) (Figure 3). Overall time to *remission* (HDRS-6 score ≤4) relapse was 11.12 weeks (SE=1.67). Those who were prior non-responders to conventional rTMS (n=11), showed about 6.5 fewer weeks of durable antidepressant *remission* [$X^2$=6.81, p=.009, mean 7.46 weeks (SE=2.83)] than those who had not previously experienced conventional rTMS (mean 13.02 weeks, SE=1.93) (Figure 4). When excluding ECT non-responders (n=6) from the group analysis, participants showed a longer period of anti-depressant durability overall (mean=15.80 weeks, SE=1.92) and in both the prior rTMS non-responder (9.83 weeks; SE=3.75) and rTMS naïve (mean=17.76, SE= 2.12) groups compared to their inclusion in the overall analysis previously reviewed.

Mixed effects multilevel models were used to assess post-treatment changes in treatment means. The longitudinal models account for both individual differences in the average depression level and individual differences in the depression trajectory across post-SAINT weeks. Differences in change from post-test to follow-up weeks were assessed using Wald $\chi^2$ with significance set at $p \leq .05$. Mean depression scores, SD, and sample size of patients who remained in the durability portion of the study are reflected in Table 4. In the acute series, all depression outcome measures showed a significant time effect over the post-SAINT follow-up time-period. HDRS-6 mean scores increased over the follow-up period, showing a significant effect of time ($\chi^2(12) = 45.4$, $p < .001$). MADRS mean scores increased over the follow-up period, showing a significant effect of time ($\chi^2(6) = 25.9$, $p < .001$). HDRS-17 mean scores increased over the follow-up period, showing a significant effect of time ($\chi^2(5) = 26.3$, $p < .001$).

**Aim 2:** Assess the relationships between durability (time to relapse) and a) time to response/remission (day 1, 2, 3, 4 or 5 of acute aiTBS), b) treatment refractoriness (Maudsley Staging Method) and c) baseline depression severity (using the MADRS, confirming with HDRS-6). It was hypothesized that 1) greater length in durability would be associated with earlier time to response/remission during the 5-day SAINT treatment series, and that 2) treatment refractoriness would have an association with longer antidepressant durability.

*Covariate/Predictor Findings*

Cox regression for survival analysis was used to investigate the effect of primary covariates 1) the Maudsley Staging Method for treatment refractoriness 2) baseline depression severity (indicated by the MADRS scale), and 3) day of response during the 5-day SAINT treatment series, on antidepressant durability (see Table 3). Each covariate was assessed in a univariate Cox regression analysis revealing the MSM as the only covariate associated with antidepressant durability [(Hazard Ratio 1.34 (95%CI: 1.012-1.768, p=0.041)]. The exponential of the coefficient for the MSM indicated that every 1-point increase in the MSM increased the hazard of relapse by 34%. Neither baseline depression severity on the MADRS scale nor day of response differentiated durability after treatment. As only one univariate predictor showed significant association with durability, a multivariate model to assess their collective impact on antidepressant durability was not needed. To explore potential demographic variable effects on durability, univariate Cox regressions were used to assess participant 1) sex, 2) age, 3) age of depression onset, and 4) illness duration influence on durability after treatment. Neither age, age of depression onset nor illness duration differentiated treatment durability (see Table 3).

*Re-treatment findings*

**Aim 3:** Explore the anti-depressant durability (time to relapse) of a second aiTBS treatment series for those who relapsed during the 6-month period. It was hypothesized that there would be a similar response durability between first and second aiTBS treatments after a previous antidepressant response, for those who experienced symptom worsening (≥25% depression score increase) and underwent a SAINT retreatment series.

Individuals who responded or remitted to SAINT and experienced a symptom reduction (≥25% decrease in HDRS-6) after their acute series of treatment were re-introduced to a second series of treatment (n=15). Kaplan-Meier survival analysis showed an overall time to event (relapse based on <50% reduction from baseline HDRS-6 score) estimate of 14.59 weeks (SE=2.56) among those who underwent re-treatment. Prior rTMS non-responders (n=5), showed fewer weeks of durable response [$X^2$=3.014, p=.083, mean 6.80 weeks (SE=2.23)] than those who had not previously experienced rTMS (mean 18.17 weeks, SE=2.81) (see Figure 5). Overall time to relapse based on remission rates was estimated at 13.97 weeks (SE=1.31). Those who previously failed TMS (n=13), again showed fewer weeks of durable remission [$X^2$=8.857, P<.003, mean 9.57 weeks (SE=1.61)] compared with those who had not previously failed TMS (n=10, mean 18.99 weeks, SE=1.57). Figure 6 shows comparable trends in mean HDRS-6 depression scores over the follow-up time period in both the acute and retreatment groups.

Mixed effects multilevel models were used to assess post-retreatment changes in depression scale means. The longitudinal models account for both individual differences in the average depression score and individual differences in the depression trajectory across post-SAINT weeks. Differences in change from post-test to follow-up weeks were assessed using Wald $\chi^2$ with significance set at $p \leq .05$. Mean depression scores, SD, and sample size of

patients who remained in the durability portion of the study are reflected in Table 3. In the retreatment group, all depression outcome measures showed a significant time effect over the post-SAINT follow-up time-period. In the retreatment group, HDRS-6 mean scores increased over the follow-up period, showing a significant effect of time ($\chi^2(13) = 35.1$, $p = .001$). MADRS mean scores increased over the follow-up period, showing a significant effect of time ($\chi^2(5) = 23.6$, $p < .001$). HDRS-17 mean scores increased over the follow-up period, showing a significant effect of time ($\chi^2(5) = 23.6$, $p < .001$).

# Chapter 5: Discussion and Conclusions

## Discussion

As the SAINT rTMS paradigm has preliminarily shown to be an efficacious and effective treatment for refractory depression with 94% response and remission rates (Cole et al., 2019), this was the first report of antidepressant durability in this sample. With standard rTMS requiring a minimum of 4-6 weeks for treatment response, and many still not responding to treatment, more paradigms are being explored. In addition to overall anti-depressant durability (time to relapse), this study also sought out to assess predictors of response to the SAINT protocol in a TRD population, including durability among those retreated with the same aiTBS protocol after experiencing symptom worsening or relapse during a 6-month follow-up timeframe. As the SAINT treatment protocol targeted a psycho-pharmacologically TRD population, prior non-responders to conventional rTMS or ECT were included to assess whether this newer rTMS paradigm might offer similar effects and antidepressant durability as compared to other paradigms such as ECT.

### *Durability*

The primary aim of this study was to describe results of antidepressant durability in a TRD cohort after receiving a 5-day aiTBS protocol. Findings from this study showed that an accelerated iTBS paradigm, such as SAINT, may produce comparable antidepressant effects as compared with prior rTMS and ECT durability studies showing relapse as early as 1-week post-ECT response (Jelovac et al., 2013). It was hypothesized that participants who previously did not respond to a conventional series of 4-6-week rTMS will relapse sooner than rTMS naïve participants. This was confirmed with the average time to relapse in the prior rTMS naïve group being more than twice as long when compared to prior rTMS non-responders. Similarly, longer

antidepressant durability trends were observed in the rTMS naïve group across both antidepressant response and remission durability survival analyses. When excluding prior ECT non-responders from the overall survival analysis of antidepressant durability after an acute series of SAINT, approximately one week was gained in anti-depressant durability in both the rTMS naïve and rTMS non-responder groups.

*Covariates/Predictors*

The second aim of this study was to explore relationships between antidepressant durability (time to relapse) and a) day of response/remission (day 1, 2, 3, 4 or 5 of acute aiTBS), b) treatment refractoriness (Maudsley Staging Method), and c) baseline depression severity (using the MADRS, confirming with HDRS-6). While assessing covariate relationships between durability (time to relapse) and possible predictors to include: 1) day of antidepressant response, 2) treatment refractoriness (MSM), and 3) baseline depression severity (MADRS), the MSM was the only significant covariate associated with antidepressant durability. These findings were contrary to the first hypothesis proposing greater length in durability being associated with earlier antidepressant response during SAINT treatment. As the MSM was the only significant covariate associated with anti-depressant durability, these findings were confirmatory of the second hypothesis proposing treatment refractoriness (MSM) would have a stronger association with antidepressant durability than baseline depression severity. As baseline depression and day of response were not significantly associated with durability, they may not be predictive of aiTBS antidepressant durability. Age, illness duration, age of depression onset, sex and illness duration were demographic covariates found to be unrelated to antidepressant durability of aiTBS. With the significant association of greater treatment refractoriness (MSM) at baseline and overall antidepressant durability, this may predict future TMS responders to accelerated

rTMS paradigms. Similarly, with less severe baseline treatment refractoriness (MSM) associated with longer post-aiTBS antidepressant durability, the use of aiTBS in the treatment of less severe/treatment resistant populations may be supported (Voigt, Carpenter & Leuchter, 2019). As baseline depression severity was not associated with aiTBS antidepressant durability, clinicians and researchers may want to consider utilizing other baseline predictors, such as the MSM, when considering which factors may predict durability treatment outcomes. As a floor effect was observed in the extremely high remission rates over 5 days of SAINT, conclusions could not be drawn as to whether acute response predicts durable outcome (Miljevic et al., 2019).

*Retreatment/Maintenance*

The third aim of this study was to assess the antidepressant durability (time to relapse) of a second aiTBS treatment series for those who experienced symptom worsening or relapse during the 6-month aiTBS acute series. All participants who were retreated after post-acute series aiTBS symptom worsening or relapse, returned to euthymia (response/remission criteria) during their second, 5-day retreatment period. Retreatment participants maintained a similar average of 14.37 weeks of durable anti-depressant response, compared with the acute series average of 14.59 weeks, confirming the hypothesis that acute and retreatment durability would show similar antidepressant durability trends. Drawing again from prior ECT continuation or maintenance studies, post-SAINT anti-depressant durability tends to repeat this pattern of durability upon continuation or reintroduction to treatment (Jelovak et al., 2013).

*Limitations*

This study had several limitations including a small sample size (n=33), reduced when comparing groups or later time-points, post-treatment; however, Kaplan-Meier survival analyses provide the ability to account for those who may never relapse or those who experience the

"event" at different time-points. As three participants are still being followed in this study, and currently meet "responder" criteria, these results could under-report of post-SAINT durability. As all re-treatment participants had previously responded to an acute series of SAINT, selection bias may be present in their subsequent response to aiTBS. Finally, as the treatment method utilized in SAINT relied on individualized mr-guided neuronavigation, the resources for these methods may not be feasible across practicing TMS clinicians; thus, limiting methodological translation.

*Future research directions*

As the clinical efficacy and refinement of rTMS have and continue to take shape, the emphasis on accelerated, spaced paradigms should be further assessed to improve time to response and anti-depressant durability. This study is the first to show an approximation of anti-depressant durability in a small, open-label sample of individuals with moderate to severe, treatment refractory MDD. Next steps include a double-blind, placebo-controlled trial of the SAINT protocol, followed by similar durability and prediction measures in an attempt to demonstrate causality by controlling for factors such as placebo effect, experimenter bias, and selection bias. Due to the exclusion of a maintenance protocol following either the acute or re-treatment SAINT series, future studies could address the potential benefits of implementing a maintenance protocol (e.g. daily or bi-weekly) which may prolong anti-depressant response and remission durability rates, as shown in prior studies (Senova et al., 2018). In large part, there remains the question as to whether reintroduction or maintenance rTMS is the most effective way to uphold the antidepressant effects of rTMS after a successful acute series.

Advancing methodological approaches by adding other biomarkers to rTMS protocols predict and/or prevent relapse may be of great benefit. For example, changes in the fcROI before

and after the SAINT protocol was collected as a potential biomarker and predictor of response and will be analyzed and reported separately. Another example may be employ future study methods allowing for fc-fMRI to be collected after each daily session over the 5-day course of treatment, which may show a potential biomarker in functional connectivity change at the day of anti-depressant response/remission. Additionally, heart rate variability (HRV) has been linked to psychopathology, and more specifically, low HRV has been associated with increased depression (Brunoni et al., 2013). Measuring HRV pre/post/follow-up rTMS may aid in the development of predicting response to rTMS, including time to relapse after an rTMS anti-depressant response. Finally, to better understand underlying mechanistic effects of rTMS, and treatment optimization, future considerations should include intentionally addressing the combination of monotherapies utilized in psychiatry not only as a way to enhance or synergize treatment effects, but also as an approach in assessing brain state and associated changes during interventions such as TMS combined with targeted psychotherapeutic engagement (Bergmann, 2018; Sathappan et al., 2019).

**Conclusions**

In conclusion, with limited data surrounding rTMS anti-depressant durability and retreatment effects, this study adds to the literature supporting the use of an accelerated, 5-day iTBS paradigm for moderate and severe TRD. Additionally, this paradigm may show equivalent efficacy for the most severe TRD populations, when compared with ECT durability. Participant acute series response and antidepressant durability may be predictive of subsequent retreatment response and antidepressant durability, and the use of the MSM may be a predictor of antidepressant durability. Overall, the SAINT paradigm may allow for faster antidepressant response, with fewer side-effects, and may be more cost effective with non-inferior durability

compared with conventional rTMS, and ECT studies (Magnezi et al., 2016). Further exploration in double-blind, RCTs will be needed to answer the many questions that remain. A priority of the field should be further assessing predictors of response while continuing to develop the best approach in maintaining anti-depressant effects after rTMS treatment response, across paradigms.

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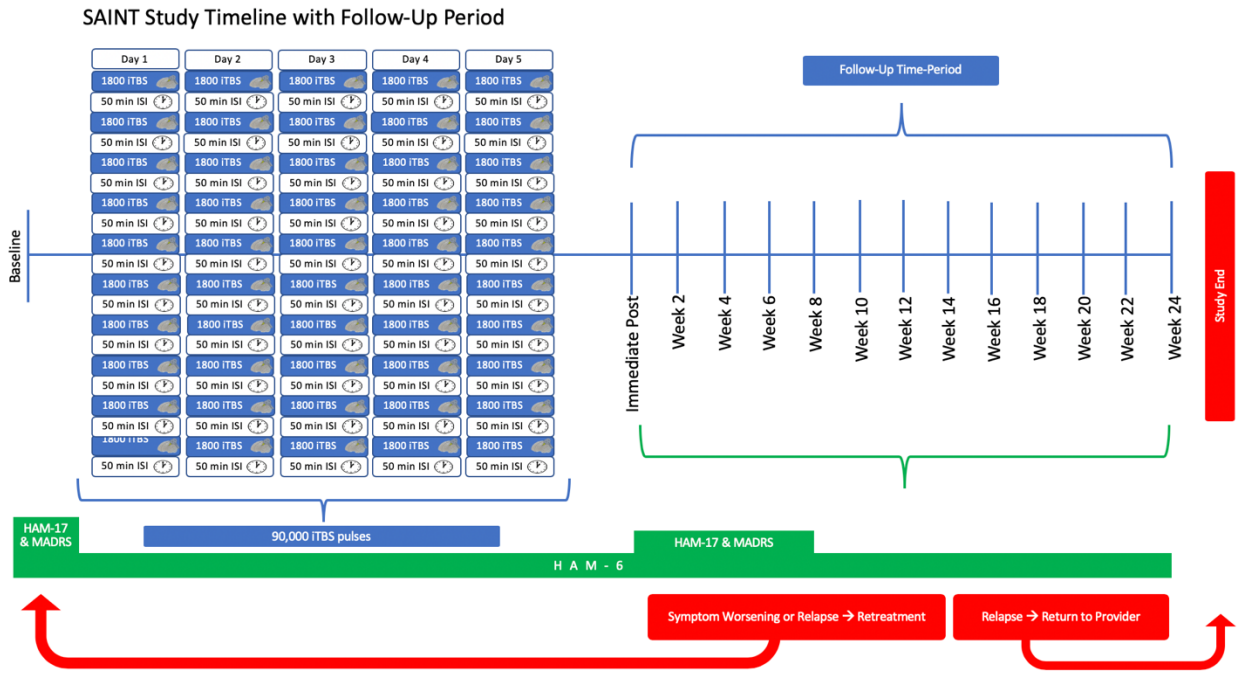
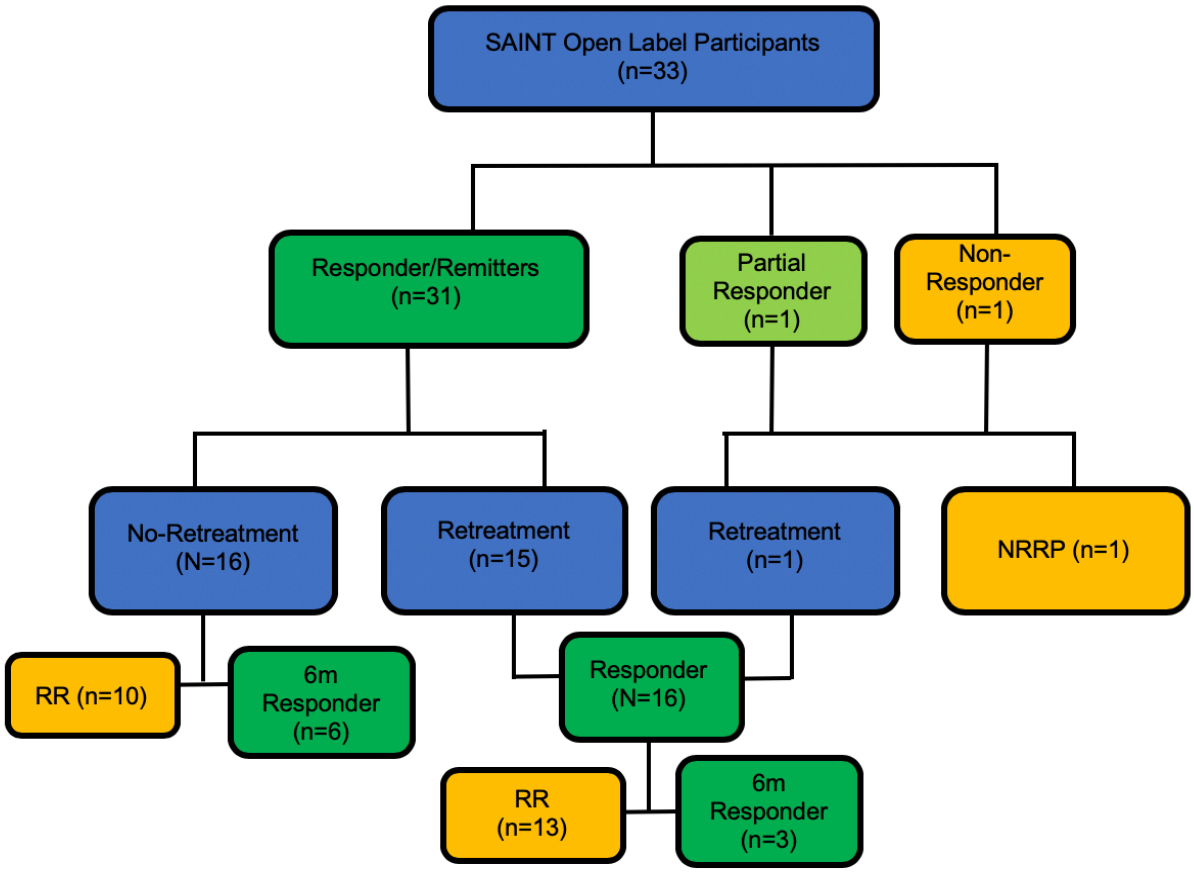



*Figure 1.* SAINT Study Timeline with Follow-Up Period
*Note.* The figure above is meant to depict the individual timeline of each participant, with indicators as to when baseline, daily and follow-up assessments were given, including process upon symptom worsening or relapse followed by either retreatment or return to provider (study end)




Abbreviations. NRRP, no response return to provider; RR, relapse and returned to provider during follow-up

*Figure 2.* SAINT Participant Study Flow Diagram

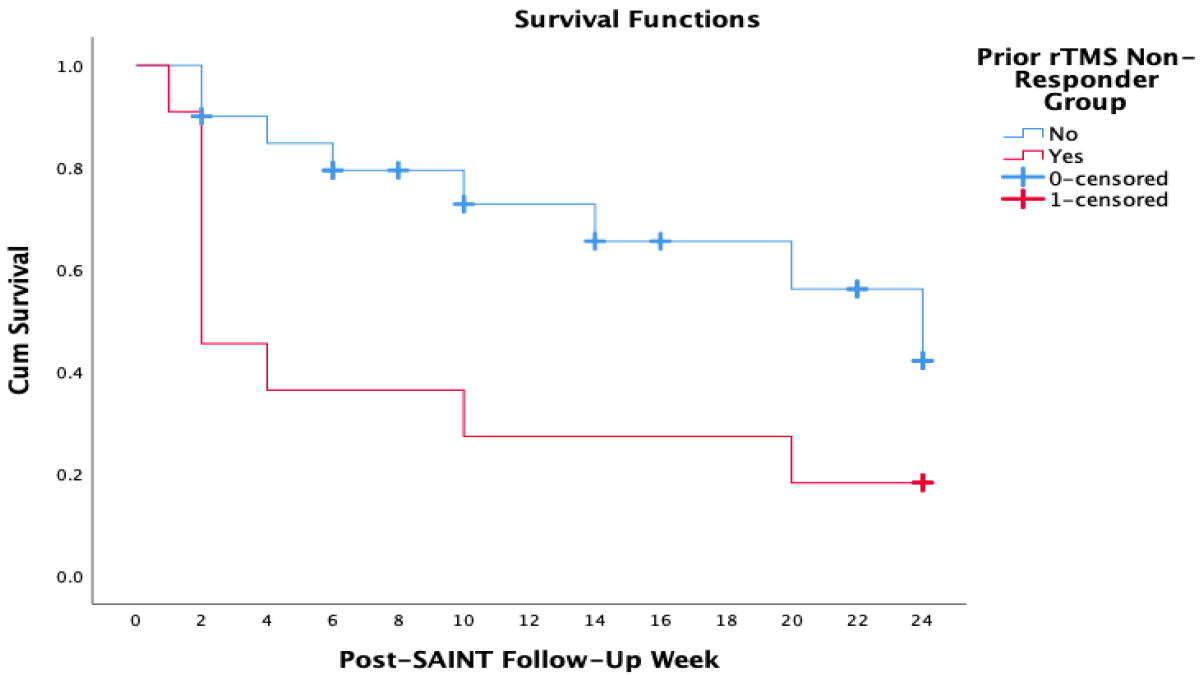



*Figure 3*. Kaplan-Meier survival curve estimate of time to week of anti-depressant response (≥ 50% increase in HDRS-6 scale) relapse over post-SAINT 24- week follow-up

*Note*. This figure shows a group comparison of prior rTMS non-responders (n=11) vs those who were rTMS naive.

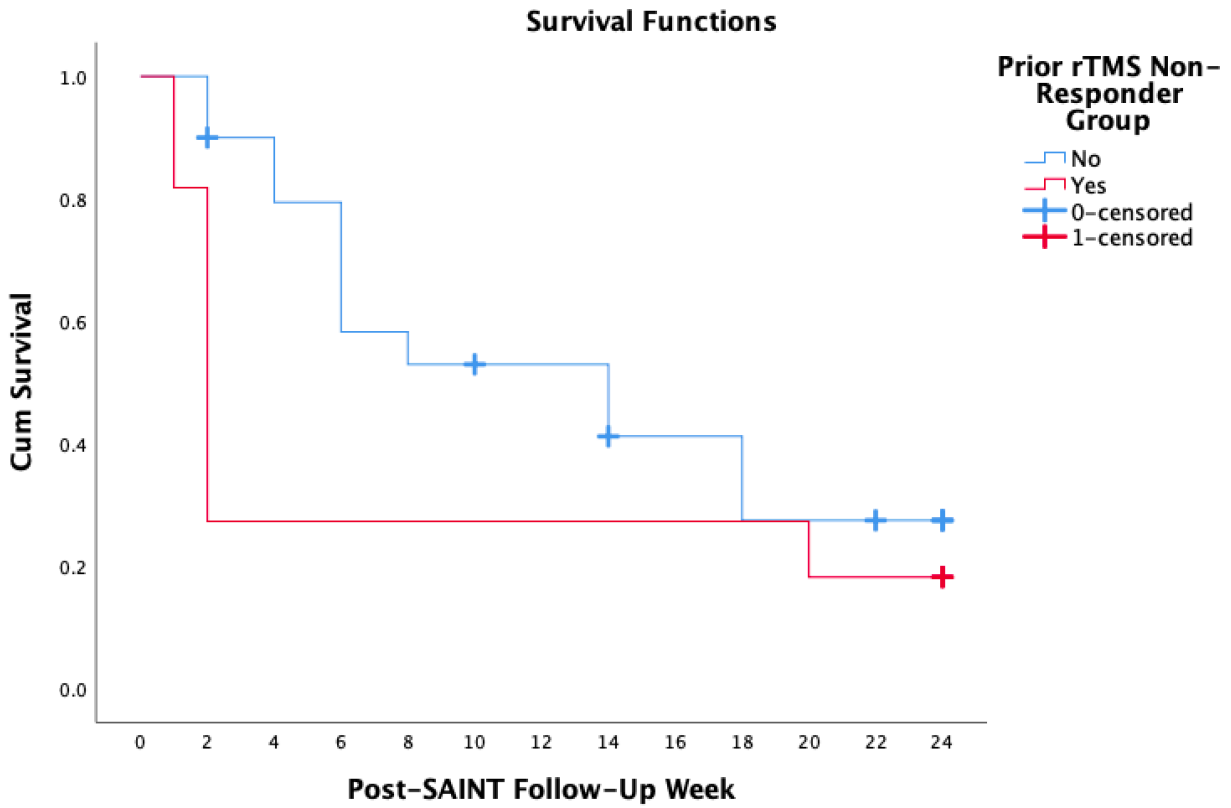



*Figure 4*. Kaplan-Meier survival curve estimate of time to week of anti-depressant remission (≥4 on HDRS-6 scale) relapse over post-SAINT 24-week follow-up
*Note*. This figure shows a group comparison of prior rTMS non-responders (n=11) vs those who were rTMS naive.

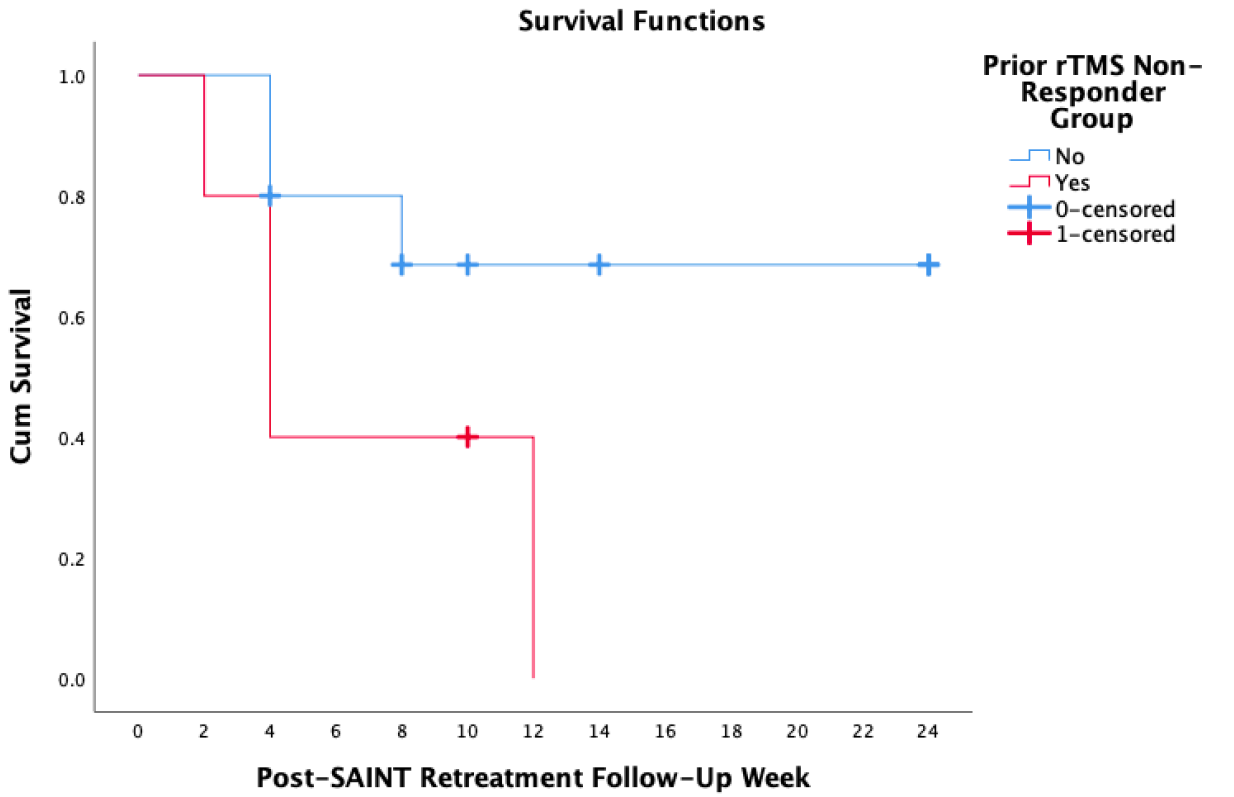
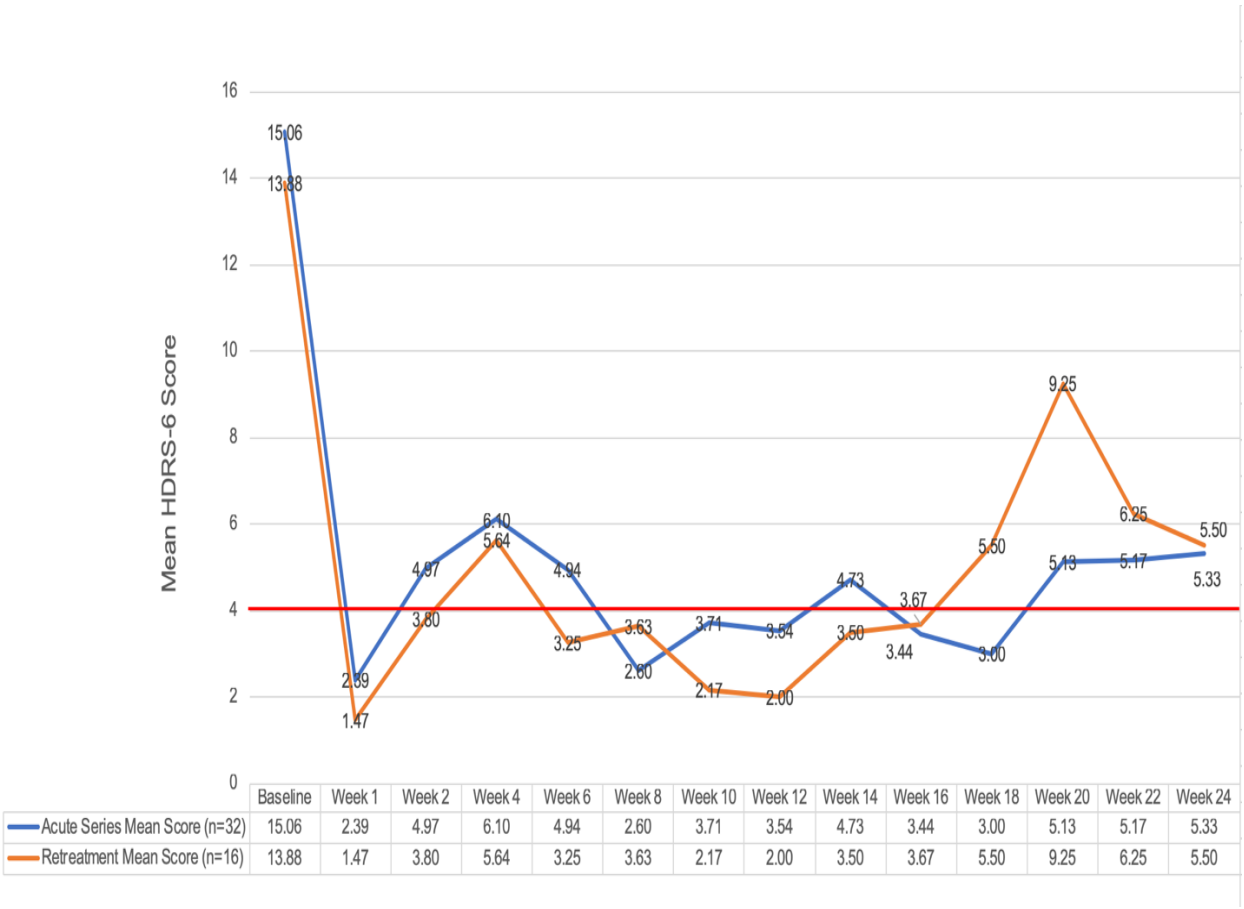



*Figure 5*. Kaplan-Meier Survival Curve Estimate of Time to Week of Anti-Depressant Response (≥ 50% increase in HDRS-6 scale) over Post-SAINT Retreatment 24-week Follow-up (n=15)




| | Baseline | Week 1 | Week 2 | Week 4 | Week 6 | Week 8 | Week 10 | Week 12 | Week 14 | Week 16 | Week 18 | Week 20 | Week 22 | Week 24 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acute Series Mean Score (n=32) | 15.06 | 2.39 | 4.97 | 6.10 | 4.94 | 2.60 | 3.71 | 3.54 | 4.73 | 3.44 | 3.00 | 5.13 | 5.17 | 5.33 |
| Retreatment Mean Score (n=16) | 13.88 | 1.47 | 3.80 | 5.64 | 3.25 | 3.63 | 2.17 | 2.00 | 3.50 | 3.67 | 5.50 | 9.25 | 6.25 | 5.50 |

*Figure 6.* Line Graph of Mean HDRS-6 Scores at Baseline and Over Post-SAINT Follow-Up Timepoints by Acute and Retreatment Groups

*Note*. The red line indicates the cut-off for remission according to the HDRS-6 criteria of ≤4.

Table 1

*Participant Demographic and Clinical Characteristics*

| Variable | |
|---|---|
| Age, years, mean (SD) | 48.70 (16.78) |
| Sex, % (*n*) male | 39.4 (13) |
| Age of Onset, years (mean) | 23.52 (11.71) |
| Illness Duration, years (mean) | 25.18 (15.86) |
| Maudsley, mean (SD) | 10.94 (2.16) |
| Prior TMS Treatment, % (*n*) | 42.4 (14) |
| Prior TMS failure | 39.4 (13) |
| Prior ECT Treatment, % (*n*) | 21.2 (7) |
| Prior ECT Failure | 18.2 (6) |
| Baseline MADRS Severity | |
| Mild | - |
| Moderate | - |
| Severe | 33.3 (11) |
| Very Severe | 66.7 (22) |
| Baseline HDRS17 Severity | |
| Mild | - |
| Moderate | 24.2 (8) |
| Severe | 75.8 (25) |
| MDD Diagnosis | 72.7 (24) |

*Note.* n=33

Table 2

*Descriptive Table of Response and Remission Over Post-SAINT Weekly Follow-Up Time-Points*

| Variable | Imm. Post | 1 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HDRS-6 | | | | | | | | | | | | | | |
| Sample size (n) | 31 | 31 | 31 | 20 | 17 | 16 | 16 | 15 | 13 | 11 | 8 | 9 | 8 | 5 |
| Responder, %(n) | 100(31) | 94(29) | 68(21) | 58(18) | 42(13) | 48(15) | 39(12) | 39(12) | 32(10) | 32(10) | 26(8) | 23(7) | 19(6) | 13(4) |
| Remitter, %(n) | 100(31) | 90(28) | 61(19) | 52(16) | 26(8) | 35(11) | 35(11) | 35(11) | 23(7) | 26(8) | 16(5) | 16(6) | 13(4) | 10(3) |

Note. Sample size varied due to relapse or retreatment. Abbreviations. Imm. Post, Immediate Post-SAINT time-point

Table 3

*Univariate Cox Regression Results of SAINT Participant Demographic and Clinical Covariates*

| Variable | Hazard Ratio (95%CI) | P-value |
|---|---|---|
| Age | 1.006 (.996-1.067) | .637 |
| Sex | .747 (.454-1.229) | .250 |
| Age Onset | 1.006 (.964-1.051) | .778 |
| Illness Duration | 1.005 (.978-1.033) | .733 |
| Maudsley Staging Method (MSM) | 1.34 (1.012-1.768) | **.041*** |
| Baseline Depression Severity (MADRS) | 1.250 (.405-3.855) | .698 |
| Day of Antidepressant Response | .773 (.524-.1.141) | .195 |

*Note*. *The only covariate associated with antidepressant durability was the Maudsley Staging Method: Significant at the $p<0.05$ level. Non-responder participant excluded (n=32).

Table 4

*Summary of Continuous Clinical Scales at Baseline and Post-SAINT 24-week Time-points*

| | Baseline | Post-SAINT | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | | | | | | | | | | | | | | |
| Sample size (n) | 32 | 32 | 30 | 29 | 18 | 16 | 16 | 15 | 13 | 11 | 8 | 9 | 8 | 5 |
| HDRS6 mean score (SD) | 15.09(2.80) | 2.09(2.74) | 4.83(5.19) | 5.86(5.66) | 4.67(4.41) | 2.44(3.39) | 3.25(4.62) | 3.07(4.40) | 4(4.65) | 3(4.07) | 2.5(2.83) | 4.78(4.21) | 3.88(5.30) | 3.6(7.0) |
| Change from immed-post (SD) | - | - | 2.73(5.11) | 3.72(6.05) | 2.28(4.84) | 0.44(3.85) | 0.75(4.97) | 1(5.18) | 1.85(5.47) | 0.73(5.26) | 0.125(4.73) | 2.56(6.06) | 1.63(7.89) | 3(7.31) |
| P value | - | - | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Sample size (n) | 32 | 32 | 30 | 29 | 17 | 14 | - | - | - | - | - | - | - | - |
| HDRS17 mean score (SD) | 27.88(5.02) | 4.28(4.63) | 8.97(8.85) | 10.76(10.39) | 8.71(8.36) | 4.79(6.45) | - | - | - | - | - | - | - | - |
| Change from baseline (SD) | - | - | 4.87(8.14) | 6.55(10.58) | 4.18(9.49) | 0.93(7.17) | - | - | - | - | - | - | - | - |
| P value | - | - | <0.001 | <0.001 | <0.001 | <0.001 | - | - | - | - | - | - | - | - |
| Sample size (n) | 32 | 32 | 30 | 29 | 16 | 13 | - | - | - | - | - | - | - | - |
| MADRS total score (SD) | 37.63(7.33) | 4.25(5.80) | 11.03(11.45) | 14.63(14.39) | 10.88(10.11) | 7.23(10.63) | - | - | - | - | - | - | - | - |
| Change from baseline (SD) | - | - | 6.5(11.05) | 9.79(15.11) | 5.56(11.16) | 2.92(11.96) | - | - | - | - | - | - | - | - |
| P value | - | - | <0.001 | <0.001 | <0.001 | <0.001 | - | - | - | - | - | - | - | - |

*Note*. Sample size varied due to relapse or retreatment. P values reflect comparison of change from immediate post-SAINT to end of treatment series score and subsequent follow-up timepoints using mixed effects multi-level models.

Table 5

*Summary of Continuous Clinical Scales at Baseline and Post-SAINT 24-week Retreatment Time-points*

| | Baseline | Post-SAINT | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | | | | | | | | | | | | | | |
| Sample size (n) | 15 | 15 | 15 | 14 | 8 | 8 | 7 | 4 | 4 | 3 | 4 | 4 | 4 | 4 |
| HDRS6 mean score (SD | 13.63(3.85) | 1.47(1.30) | 3.8(4.02) | 5.64(5.46) | 3.25(2.83) | 3.63(5.21) | 2.42(2.82) | 2(4) | 3.5(3.42) | 3.67(6.35) | 5.5(5.57) | 9.25(10.90) | 6.25(4.5) | 5.5(4.93) |
| Change from immed-post (SD) | - | - | 2.25(3.80) | 4.15(5.80) | 1.63(2.13) | 2.25(4.33) | .83(1.72) | .75(2.99) | 1.75(3.30) | 2.67(4.62) | 4.25(4.19) | 8(9.76) | 5(3.92) | 4.25(3.77) |
| P value | - | - | <0.001 | <0.001 | <0.001 | <0.001 | 0.002 | 0.005 | 0.003 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Sample size (n) | 15 | 15 | 15 | 13 | 7 | 4 | - | - | - | - | - | - | - | - |
| HDRS17 mean score (SD) | 25.87(6.91) | 2.6(2.20) | 7.47(5.79( | 10.77(10.85) | 6.57(4.69) | 8.75(8.96) | - | - | - | - | - | - | - | - |
| Change from baseline (SD) | - | - | 5.14(5.19) | 4.5(8.06) | 4.43(2.82) | 7.25(7.72) | - | - | - | - | - | - | - | - |
| P value | - | - | <0.001 | <0.001 | 0.003 | <0.001 | - | - | - | - | - | - | - | - |
| Sample size (n) | 15 | 15 | 15 | 14 | 6 | 4 | - | - | - | - | - | - | - | - |
| MADRS total score (SD) | 35.27(8.56) | 2.8(3.05) | 10.68(10.90) | 13.21(13.41) | 7(5.48) | 12.75(11.24) | - | - | - | - | - | - | - | - |
| Change from baseline (SD) | - | - | 8.27(10.26) | 10(13.24) | 3.83(3.92) | 9(10.03) | - | - | - | - | - | - | - | - |
| P value | - | - | <0.001 | <0.001 | 0.028 | <0.001 | - | - | - | - | - | - | - | - |

*Note*. Sample size varied due to relapse. P values reflect comparison of change from immediate post-SAINT to end of treatment series score and subsequent follow-up timepoints using mixed effects multi-level models.

# Appendices

## Appendix A

*Maudsley Staging Method Parameters and Scoring Convention*

| Parameter/dimension | Parameter categories | Score |
|---|---|---|
| Duration | | |
| | Acute (≤12 months) | 1 |
| | Sub-acute (13–24 months) | 2 |
| | Chronic (> 24 months) | 3 |
| Symptom severity | | |
| *(At baseline)* | Subsyndromal | 1 |
| | Syndromal | |
| | Mild | 2 |
| | Moderate | 3 |
| | Severe without psychosis | 4 |
| | Severe with psychosis | 5 |
| Highest score for illness dimensions | – | 8 |
| Overall maximum score for MSM | | 15 |
| Severity score categories of the MSM | Severity range | 3–15 |
| | Mild | 3–6 |
| | Moderate | 7–10 |
| | Severe | 11–15 |

**Appendix B**

*The Hamilton Rating Scale for Depression (HDRS-17)*

**The Hamilton Rating Scale for Depression (HDRS) - 17**

Patient ID: _____ 17-item total:_____
Date: _____
Session #:_____
Rater:_____

1. **Depressed Mood** (Sadness, hopeless, helpless, worthless)*

    0. Absent
    1. Mild: (Feels depressed no more than 2 days)
    2. Moderate: (Feels depressed more days than not, or missed work 1 day, or suicidal ideation 1 day)
    3. Marked: (Communicates feeling states non-verbally – i.e., through facial expression, posture, voice, and tendency to weep, OR Depressed more days than not, and missed 2 days of work/activities or suicidal ideation 2 days)
    4. Severe: (Patient reports VIRTUALLY ONLY these feeling states in his/her verbal and nonverbal communication, OR Depressed almost every day, and missed work/activities 3 or more days or suicidal ideation 3 or more days)

---

2. **Feelings of Guilt***

    0. Absent
    1. Self-reproach, feels s/he has let people down.
    2. Ideas of guilt or rumination over past errors or sinful deeds.
    3. Present illness is a punishment. Delusions of guilt.
    4. Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

---

3. **Suicide** (***initial items in box to the left if pt. endorses suicidal ideation to denote that they were assessed; tell treating psychiatrist and supervisor; if both are unavailable, tell study coordinator)

    0. Absent
    1. Feels life is not worth living
    2. Wishes s/he were dead or any thoughts of possible death to self (e.g., has thought about it but would not do it because of the kids)
    3. Suicidal ideas or gestures (e.g., definite plan, small cuts, hangs noose but does not go through with it, plays Russian Roulette with no bullets)

4. Attempt at suicide during the past week (any attempt rates 4 whether planned or not – e.g., Russian Roulette with bullets)

---

**4. Insomnia – Early**

0. No difficulty falling asleep (or difficulty only 1 night)
1. Complains of occasional difficulty falling asleep (i.e., more than ½ hour on 2 to 3 nights)
2. Complains of nightly difficulty falling asleep (i.e., more than ½ hour on 4 or more nights)

---

**5. Insomnia – Middle**

0. No difficulty (or difficulty only 1 night)
1. Patient complains of waking up/being restless and disturbed during the night on 2 or 3 nights
2. Waking up/being restless and disturbed during the night on 4 or more nights – any getting out of bed rates 2 (except for purposes of voiding)

---

**6. Insomnia – Late** (last two hours of expected sleep)

0. No difficulty (or difficulty only 1 night)
1. Waking in early hours of the morning but goes back to sleep (2 or 3 nights)
2. Unable to fall asleep again if s/he gets out of bed (4 or more nights)

---

**7. Activities (School, Work, Friends, Household, Hobbies, etc.)***

0. No difficulty
1. Thought and feelings of incapacity, fatigue, or weakness related to activities, work, or hobbies (i.e., loss of interest/decreased pleasure in work/other significant activities, but does not have to push oneself to do them)
2. Loss of interest in activity, hobbies, or work – either directly reported, or indirect in listlessness, indecision, and vacillation (feeling of having to push oneself to do them)
3. Decrease in actual time spent in activities or decrease in productivity
4. Stopped working because of present illness (i.e., stopped engaging in any important domain of activity in the last week)

---

**8. Psychomotor Retardation** (slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

0. Normal speech and thought
1. Slight retardation at interview (i.e., movement, gesture, or verbal latencies are mildly slowed, but barely noticeable; there is <u>no interference</u> with the pace of the interview)

2. Obvious retardation during interview (i.e., sighing, obvious difficulty concentrating and answering questions, and movement is somewhat forced and difficulty; some interference with the pace of the interview)
3. There is significant/great interference with the pace of the interview; interview is almost impossible to conduct.
4. Complete stupor

---

**9. Psychomotor Agitation**

0. Normal thought, speech, and behavior
1. Slight fidgetiness (i.e., occasionally moving part(s) of body such as finger tapping, or playing with pencil or other inanimate objects, etc.)
2. Obvious "playing with" hands, hair, etc., (and mild difficulty sitting still; the pace of the interview is not interrupted)
3. Moving about; can't sit still (and moving whole torso, getting up from chair, etc.; some interference with the pace of the interview)
4. Hand-wringing, nail-biting, hair-pulling, biting of lips, rubbing legs, pacing or walking about, etc. (normal pace of the interview is significantly/greatly affected)

---

**10. Anxiety – Psychic** (anxiety/worry should be over and above what would be expected given patient's current circumstances)*

0. No difficulty
1. Subjective tension and irritability (i.e., free-floating anxiety)
2. Meets criteria for (1), worrying about minor matters (i.e., a specific concern such as a child's grades), and mild for 3 or less days in the last week
3. Meets criteria for (2), apprehensive attitude apparent in face or speech (e.g., furrowed brow), and moderate for 4 or more days in last week
4. Meets criteria for (3), fears expressed without questioning, and severe for 4 or more days in last week

---

**11. Anxiety – Somatic** (physiological concomitant of anxiety; **Do not rate if medication or treatment side effect**)

Gastrointestinal: (indigestion, gas, diarrhea, stomach cramps, belching)
Cardiovascular: (palpitations, headaches)
Respiratory: (hyperventilation, sighing)
Urinary frequency
Sweating, flushing, tremor

0. Absent (or only 1)
1. Mild (2 days)

2. Moderate (3 to 4 days)
3. Marked (almost every day)
4. Severe (i.e., interference with work, social, or family functioning)

---

**12. Somatic Symptoms – Gastrointestinal** (i.e., Appetite)

Comment: This item should be rated solely on the basis of loss of appetite. Rate gastrointestinal problems under item 11, Anxiety – Somatic.

0. None
1. Loss of appetite but eating without encouragement from others. Food intake about normal
2. Difficulty eating without urging from others. Marked reduction of appetite and food intake

---

**13. Somatic Symptoms – General***

0. None
1. Heaviness in limbs, back, or head. Backaches, muscle aches. Loss of energy and fatigability (i.e., mild and present most of the day for 1 to 3 days)
2. Any clear-cut symptom rates 2 (i.e., moderate to severe OR present for more than 3 days)

---

**14. Genital Symptoms** (symptoms such as loss of libido, menstrual disturbances)

0. Absent (normal interest)
1. Mild or Moderate (some disinterest noticed)
2. Severe (no interest during the past week)

---

**15. Hypochondriasis**

0. No symptoms present
1. Self-absorption (mild somatic concerns that are non-specific and fleeting)
2. Preoccupation with health (brooding and preoccupation with specific concerns more days than not)
3. Frequent complaints, requests for help, etc. (because of health concerns)
4. Hypochondriacal delusions (e.g., “I have leukemia.” in the absence of a doctor’s diagnosis)

---

**16. Loss of Weight** (please compare this visit’s weight with last visit’s weight)

0. No weight loss
1. Probably weight loss associated with the present illness (up to 2 lbs.)
2. Definite weight loss associated with the present illness (more than 2 lbs.)

---

**17. Insight**

0. Acknowledges being depressed and ill (or not currently depressed)
1. Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc. (i.e., denial)
2. Denies being ill at all

---

**Questions 1, 7, 10, 13, 2 and 8 are used to comprise the HDRS-6 Scale*

## Appendix C

## MONTGOMERY-ASBERG DEPRESSION RATING SCALE (MADRS)

Stanford University School of Medicine
Department of Psychiatry

Total Score:_____

**MONTGOMERY-ASBERG DEPRESSION RATING SCALE (MADRS)**

Instructions

- The ratings should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0,2,4,6) or between them (1,2,3) & then check the box next to the appropriate number.
- It is important to realize that it is only on a rare occasion that a depressed patient is encountered who cannot be rated on the items in the scale. If definite answers cannot be elicited from the patient, all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice.
- The items should be rated with regard to how the patient has done **over the past week.**

---

1. **Apparent Sadness** – Despondency, gloom & despair (more than just ordinary transient low spirits) reflected in speech, facial expression, & posture. Rate by depth and inability to brighten up.

   (0) No sadness.
   (1) -
   (2) Looks dispirited but does brighten up without difficulty.
   (3) -
   (4) Appears sad & unhappy most of the time.
   (5) -
   (6) Looks miserable all the time. Extremely despondent.

2. **Reported Sadness** – Reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to by influence of events.

   (0) Occasional sadness in keeping with the circumstances.
   (1) -
   (2) Sad or low but brightens up without difficulty.
   (3) -
   (4) Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   (5) -
   (6) Continues or unvarying sadness, misery or despondency.

3. **Inner Tension** – Feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration & the extent of reassurance needed.

   (0) Placid. Only fleeting inner tension.
   (1) –
   (2) Occasional feelings of edginess & ill-defined discomfort.
   (3) –
   (4) Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   (5) –
   (6) Continuous or unvarying sadness, misery or despondency.

4. **Reduced Sleep** – Experience of reduced duration or depth of sleep compared to subject's own normal well pattern.

   (0) Sleeps as usual.
   (1) –
   (2) Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
   (3) –
   (4) Sleep reduced or broken by at least 2 hours.
   (5) –
   (6) Less than 2 or 3 hours of sleep.

5. **Reduced Appetite** – Feelings of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

   (0) Normal or increased appetite.
   (1) –
   (2) Slightly reduced appetite.
   (3) –
   (4) No appetite. Food is tasteless.
   (5) –
   (6) Needs persuasion to eat at all.

6. **Concentration Difficulties** – Difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

   (0) No difficulties in concentrating.
   (1) –
   (2) Occasional difficulties in collecting one's thoughts.
   (3) –
   (4) Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
   (5) –
   (6) Unable to read or converse without great difficulty.

7. **Lassitude** - Difficulty getting started or slowness initiating and performing everyday activities.

   (0) Hardly any difficulty in getting started. No sluggishness.
   (1) –
   (2) Difficulties in starting activities.
   (3) –
   (4) Difficulties in starting simple routine activities which are carried out with effort.
   (5) –
   (6) Complete lassitude. Unable to do anything without help.

8. **Inability to Feel** – Subjective experience of reduced interest in the surrounding, or activities that normally give pleasure. The ability to react with adequate emotion to circumstance or people is reduced.

   (0) Normal interest in surroundings and in other people
   (1) –
   (2) Reduced ability to enjoy usual interests.
   (3) –
   (4) Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
   (5) –
   (6) The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. **Pessimistic Thoughts** – Having thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

   (0) No pessimistic thoughts.
   (1) –
   (2) Fluctuating ideas of failure, self-reproach or self-depreciation.
   (3) –
   (4) Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
   (5) –
   (6) Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakeable.

10. **Suicidal Thoughts** – Feelings that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicide attempts should not in themselves influence the rating.

    (0) Enjoys life or takes it as it comes.
    (1) –
    (2) Weary of life. Only fleeting suicidal thoughts.
    (3) –
    (4) Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
    (5) –
    (6) Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

## Appendix D

*MRI Scanning and rTMS Stimulation Safety Questionnaire*

SCANNING AND STIMULATION SAFETY

1. Would you agree to have an MRI scan? Yes No
2. Have you ever had any form of Transcranial Magnetic Stimulation (TMS)? Yes No
3. Have you ever had an adverse reaction to TMS? Yes No
4. Please provide any details of any adverse reactions to TMS:
5. Would you agree to receive repetitive Transcranial Magnetic Stimulation (rTMS)? Yes No
6. Have you ever had an EEG? Yes No
7. Do you have any personal or family history of epilepsy, convulsions, or seizures? Yes No
8. Please provide details of any personal or family history of epilepsy, convulsions or seizures:
9. Do you suffer from frequent or severe headaches? Yes No
10. Please provide details of any frequent or severe headaches
11. Have you ever had any other brain related condition? Yes No
12. Please provide details of any other brain related condition?
13. Have you ever had any illness that caused a brain injury? Yes No
14. Please provide details of any illness that caused a brain injury?
15. Do you have tattoos (especially near the head) or "permanent makeup" (e.g. tattooed eyeliner or eyebrows)? Yes No
16. Regarding your tattoos, please provide the appropriate location and size of each:
17. Do you have any piercings that cannot be removed? Yes No
18. Please explain where the piercings are located and why you are unable to remove them:
19. Do you have ANY metal in the body other than dental fillings (e.g. orthodontic braces, permanent retainers, joint pins, or shrapnel)? Yes No
    Indicate the approximate location and size of each. Also, please specify the dates of surgery
20. Do you have a pacemaker or implanted devices (e.g. IUDs, breast implants, cochlear implants, neurostimulators, intracardiac lines)? Yes No
21. Indicate pacemaker/implant location, size, purpose, composition, manufacturer, date placed in body, and country of procedure. If you have an IUD, please indicate the name of the IUD and the material from which it was made.
22. Have you ever worked with metal (as a machinist or as a hobby)? Yes No
23. Indicate metal exposure date, duration, frequency, and if goggles were worn. Please indicate if there were any injuries to the eyes during this time.
24. Are you pregnant? Yes No
25. Do you plan on getting pregnant in the next year? Yes No