A Pilot Study of iTBS in Bipolar I Depression

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Summary of Revisions Made: Made minor revisions to wording of inclusion criteria and recruitment procedures. Also fixed grammatical and spelling errors

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Summary of Revisions Made: Minor revisions to treatment details (see 5.1) and methods for assessing adverse events related to suicide assessments (see 7.1)

Version Number: 1.5
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Summary of Revisions Made: Removal of some self-report instruments (see 6.2) that will be given to patients. Description of instruments (see 6.3) has been updated accordingly.

Version Number: 1.6
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Summary of Revisions Made: Updated adverse event reporting procedures (see 7.3) to include reporting to TMS device manufacturer. Changed age range in inclusion criteria (see 4.1) and added pre-consent screening instrument (see 4.3)

Version Number: 1.7
Version Date: 23 Mar 2023
Summary of Revisions Made: Made various updates to timing and inclusion of certain study evaluations to better capture patient symptom change (see 6.2). Changed definition of immediate follow up throughout entire protocol (changed from 3-5 days to up to 5 days). Made consistent/clarified instruments that assess suicidality (see 7.1). Updated age in study synopsis to be consistent with inclusion/exclusion criteria

Version Number: 1.8
Version Date: 19 Apr 2023
Summary of Revisions Made: Updated schedule of screening visit to all participant's to be on a sufficient medication or medication dose as required by inclusion criteria 4 and 5 (see 6.1, 6.2). Participant reimbursement method is further specified (see 3).

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STUDY SYNOPSIS

Title	A Pilot Study of iTBS in Bipolar I Depression
Source of Funding	Baszucki Brain Research Fund
Study Population	Participants aged 18+ years old with a diagnosis of bipolar I disorder, current episode depressed
Study Design	A multisite, open label pilot study to investigate the efficacy and safety of a novel accelerated intermittent theta-burst stimulation (iTBS) protocol while assessing for changes in neuroimaging biomarkers associated with treatment response
Primary Objectives	To examine the use of accelerated iTBS to treat symptoms of treatment resistant depression in bipolar I disorder and assess changes in neuroimaging biomarkers that may predict treatment response.
Number of Sites	2
Total number of Participants	10 (5 at each site)
Study Duration	1 year

ABSTRACT

Intermittent theta-burst stimulation (iTBS) is a patterned form of repetitive transcranial magnetic stimulation (rTMS), an effective, neuromodulatory treatment for refractory depression. Accelerated rTMS paradigms have become of increasing clinical interest to address the potential limiting factors of dose response variability and the burden that standard rTMS treatment poses due to the requirement of weeks of treatment at great financial expense. Even with reduced treatment time in iTBS compared with standard rTMS, there remains a barrier in requiring weeks or months of daily treatment sessions for desired response. A recent study carried out by members of our collaborative study team assessed the safety, tolerability and efficacy of an accelerated iTBS protocol and found a 90% antidepressant response in individuals with treatment resistant depression (TRD), in only 5 days (Cole et al., 2020, 2022) This proposed pilot study intends to use this novel accelerated iTBS approach for TRD in bipolar disorder, while assessing changes in neuroimaging biomarkers that are associated with treatment response. It will provide feasibility data to lead to development of a larger, multisite, adequately powered study of this treatment approach and factors associated with treatment response through collaborations within nodes of the National Network of Depression Centers (NNDC), a consortium of academic centers of excellence providing care for participants with mood disorders.

1. STUDY OBJECTIVES

1.1 Primary Objective

To examine the use of accelerated iTBS to treat symptoms of treatment resistant depression in bipolar I disorder and assess changes in neuroimaging biomarkers that may predict treatment response:

Primary Outcome Measure: Change in Montgomery-Asberg Depression Rating Scale (MADRS) score.

Secondary Outcome Measure: Changes in MRI derived functional connectivity of the subcallosal cingulate to the DLPFC and within the default mode network.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Bipolar disorder is a chronic and burdensome illness that affects up to 5% of adults (Merikangas et al., 2011) and is associated with direct and indirect costs of care exceeding $200 billion annually in the US (Cloutier et al., 2018). Individuals with bipolar disorder spend considerably more time ill with depression than with mania or hypomania symptoms (Miller et al., 2014), such that depression accounts for the majority of the time spent unwell. Bipolar disorder is associated with high rates of morbidity and mortality and is an important contributor to long-term dysfunction due to psychosocial impairment, loss of work productivity and high rates of substance abuse (McIntyre & Calabrese, 2019). Compared to the general population, individuals with bipolar disorder are at greater risk to attempt and complete suicide, especially among individuals experiencing longer periods of depression than mania (Baldessarini et al., 2006). First line treatments for depression are limited in bipolar disorder, and treatment resistance can be up to two times higher when compared to unipolar depression (Tondo et al., 2014).

2.2 Study Rationale

Repetitive transcranial magnetic stimulation (rTMS) is a safe, neuromodulatory clinical intervention used to treat depression. When stimuli are applied to the left dorsolateral prefrontal cortex (LDLPFC), rTMS has been shown to be safe and effective in treating individuals with both unipolar and bipolar depression (Kazemi et al., 2018; Rachid et al., 2017). Accelerated rTMS paradigms have recently been explored to determine the safety, tolerability, and efficacy of delivering multiple sessions over fewer days, to achieve similar outcomes compared with a standard series of rTMS (Sonmez et al., 2019). Reducing treatment time is important not only to reduce individuals' suffering and resource strain, but also to address accelerating antidepressant response in more severely depressed individuals who are at greater risk for suicide. Intermittent theta burst stimulation (iTBS) is a form of patterned rTMS, recently deemed "non-inferior" to standard rTMS in the treatment of unipolar major depressive disorder (Blumberger et al., 2018; Chung et al., 2015). Even with a significant benefit in reduced treatment time in iTBS compared with the standard rTMS treatment time of 4-6 weeks, time constraints, transportation, and the financial resources to attend daily sessions over weeks of time remain cumbersome limitations (Bakker et al., 2015). Moreover, as individuals with bipolar disorder tend to have more treatment resistance and spend more time in a depressed state with higher risk for suicide the value of non-invase treatment options is emphasized.

A recent study carried out by members of our collaborative study team developed an accelerated iTBS treatment paradigm called Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT). SAINT utilized prior evidence to further enhance the

propensity of antidepressant response to iTBS by modifying parameters in pulse spacing, dosage and treatment target location (Cazzoli et al., 2009, 2012; Fox et al., 2012; Gamboa et al., 2010; Noh et al., 2012). Applied in a sample of individuals with unipolar (n=20) and bipolar (n=5) treatment resistant depression (TRD), the use of an accelerated iTBS paradigm yielded approximately 90% response and remission rates in depressive symptoms, in both unipolar and bipolar TRD participants (Cole et al., 2020). Of the 5 bipolar TRD participants, all met depression remission criteria within 5 days of treatment, with no hypomania/mania conversion observed during treatment or at follow-up. More recently, SAINT demonstrated evidence of efficacy over sham stimulation in RCT for treatment-resistance depression (Cole et al., 2022). The current study aims to further evaluate the use of an adapted accelerated iTBS protocol for bipolar TRD and neuroimaging biomarkers of treatment response. It will leverage the resources of the National Network of Depression Centers (NNDC), a consortium of academic centers of excellence caring for participants with depression and bipolar disorder, to conduct the pilot study.

3. STUDY DESIGN

In order to establish feasibility of study design and approach, we will conduct an open label pilot trial of treatment using accelerated iTBS over the left dorsolateral prefrontal cortex (LDLPFC) (up to five days, up to 10x/day) using the MagVenture MagPro X100 rTMS System. Participants will have individualized treatment targets that will be produced from structural and functional MRI scans using the software services of Magnus Medical. We will enroll a total of 10 outpatient participants at two participating NNDC centers, the Johns Hopkins University and University of Texas at Austin. The participants will be diagnosed with bipolar I disorder, currently depressed, as determined by a SCID-5 assessment at screening [Day -5/-14]. Participants will be asked to remain on their psychotropic medications for stabilization throughout the screening, baseline, active study and follow-up phases of the study. During active study, changes in medication dosages may be made based on clinical judgment as outlined below. Participants will be required to have an established psychiatrist in order to facilitate ongoing care after the trial.

The expected overall study duration is one year. Each patient will have up to 9 total visits over the course of one month. One visit for consent and screening. One visit for baseline clinical and self-report assessments, MRI scan, and neurocognitive tests. Five consecutive day visits (or less per symptom remission as outlined above via MADRS </=10) of 10 hours each for treatment. Two visits for follow-up. One immediately (up to 5 days) after last day of treatment for clinical and self-report assessments, MRI scan, and neurocognitive tests. And another visit 1-month post-treatment visit for clinical and self-report assessments. All costs for the clinical assessments, MRI scans and TMS treatment related to the conduct of the study will be covered by the study at no expense to the patient. Participants will receive $500 compensation upon completion of last follow up appointment. This study will offer participants a choice to receive payment/reimbursement through the JHU Greenphire ClinCard Program. The standard Greenphire information sheet will be used to explain the use of Greenphire to participants.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

1. 18+ years of age
2. Bipolar I disorder diagnosis as defined by The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)
3. Currently experiencing a Major Depressive Episode with Montgomery-Asberg Depression Rating Scale (MADRS) >/= 20 at screening [Day -5/-14] and baseline [Day 0]
4. On a stable and adequate dose of an anti-manic agent (Lithium with a level of at least 0.6, Depakote with a level of at least 50, or a therapeutic dose of carbamazepine, oxcarbazepine, or a neuroleptic for treatment of mania per clinician judgment) without dose changes for at least 6 weeks prior to the active study time period. Final assessment of appropriateness of participant's pharmacologic regimen is subject to study team clinician judgment.
5. Having failed a therapeutic trial of a first line bipolar depression antidepressant (as specified by the Antidepressant Treatment History Form and updated with new medications approved by the FDA for treatment of bipolar depression) in this current episode. This includes a minimum 4 week trial of one of the following medications (minimum dosage): lithium 900mg daily (or blood level >= 0.6 mEq/L), carbamazepine 400mg daily (or blood level >= 0.8 mEq/L), lamotrigine 200mg daily, asenapine 20mg daily, lurasidone 20mg daily, olanzapine 10mg daily, quetiapine 300mg daily, or lumateperone 42mg daily. Final determination of a failed adequate therapeutic trial is subject to study team clinician judgement.
6. Established outpatient psychiatrist

4.2 Exclusion Criteria

1. Female that is pregnant or breastfeeding, or of childbearing potential but not using medically acceptable birth control during study
2. Current mixed episode assessed by clinician judgment as defined by DSM-5 criteria
3. Current active substance use disorder (as defined by DSM-5) with exception of nicotine and caffeine. Participants may be subject to urine drug screen base on study team clinician judgment.

4. Participation in any clinical trial with an investigational drug or device within the last 3 month or concurrent to study participation
5. History of epilepsy, shrapnel or metal in the head or skull, cardiovascular disease/event, OCD, or autism spectrum disorder
6. Clinically defined major neurological disorder; including, but not limited to, seizure disorder and history of loss of consciousness due to head injury for greater than 10 minutes, or documented evidence of brain injury
7. Active suicidal risk based on investigator's clinical judgment
8. Clinically significant unstable medical condition
9. Other condition judged by investigator that could prevent the participant from completion of the study (such as but not limited to, significant physical disability (e.g., hearing/visual deficits) to perform a neutral memory task and/or neuropsychological test battery)
10. Ferromagnetic metal implant or another contraindication to imaging in a 3 Tesla MRI
11. ECT treatment in the past 3 months
12. Minimum of 6 months since last manic or hypomanic episode as defined by DSM-5 criteria

4.3 Study Enrollment Procedures

At Johns Hopkins University, participants will be recruited through clinics affiliated with the Johns Hopkins Mood Disorders Center in the Department of Psychiatry and Behavioral Sciences, or they may be referred to the study by other Johns Hopkins and community physicians. Clinicians will consider potential patients who meet inclusion/exclusion criteria and discuss the study with them. Then, the clinician or patient may contact the study team to schedule a meeting to undergo the consent and formal screening process. Once a study team member has been contacted, they may send potential participants a pre-consent screener via REDCap survey. This screener focuses on basic questions to establish whether the individual may be eligible to participate in the study. A copy of the screener is included with this application. The screener will explain why we are asking these questions and will inform the individual that their responses are completely voluntary. The screener will also inform the individual that any information we collect on them will be permanently removed if they decide not to participate in the study or are not eligible to participate.

At University of Texas at Austin, participants will be recruited through the UT Health Austin Bipolar Disorder Center. UT Austin and community physicians may also refer patients who may be eligible to participate in this study.

At both sites, the consenting and clinical screening assessment will be preformed in-person in a private office setting, or virtually by secure audio/video platform as works best for the individual and current COVID environment. Only after the consenting process will patient medical records be reviewed as provided by patient or patient's mental health provider.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Device Rationale:
In our study, iTBS will be delivered using the Magnus Transcranial Magnetic Neuromodulation System (MNS). MNS consists of the MagVenture MagPro X100 rTMS Stimulator System (Magventure A/S, Denmark) equipped with a MagVenture Cool-B65 coil. A Localite neuronavigation system (Localite GmbH, Sankt Augustin, Germany) will be used to position the TMS coil over the individualized stimulation target at each session. MagVenture has a 40+ history in the development of safe and reliable TMS stimulators which have widespread clinical and research use. We will follow the dosing that was used successfully in the prior SAINT study carried out by members of our collaborative study team. This is the same equipment that has been used for all published SAINT clinical trials to date.

Traditional 10Hz TMS treatment is on label for the MagVenture MagPro X100 device we are using. Theta burst with an X100 is FDA cleared for treatment of MDD (K173620). No TMS is FDA cleared yet for treating bipolar depression. So, we are using a TMS machine that is FDA-cleared for treating MDD, but for a non-FDA-cleared indication, bipolar depression.

Theta burst stimulation (iTBS) is minimal risk because the risk of seizure is very low (only reported once in literature) and there is no other risk other than minimal scalp irritation. We are using iTBS with “off label” stimulation parameters which have a lower risk profile than the on label approved parameters. Specifically, these parameters include: 1) 1800 pulses of iTBS (600 was in clearance, but only 1800 has been shown to work in a blinded RCT), 2) 10 session per day instead of 1, 3) 90,000 overall pulses instead of 18,000 total, 4) 5 days instead of 36, 5) 90% depth adjusted intensity instead of 120% non-depth adjusted, and neuronavigated targeting. The increased dose and dose density increases the risk, the lower stimulation intensity, fewer days, and navigated targeting all reduce risk.

Treatment Details:
Motor threshold: Using single pulse TMS, the scalp position of lowest motor threshold for the left first dorsal interosseous or abductor pollicis brevis muscles will be determined. Resting motor threshold (MT) will be defined by the lowest power setting producing a visible muscle contraction in ≥5 of 10 trials.

rTMS system and treatment: For this study, we will be using the the MagVenture MagPro X100 rTMS Stimulator System (Magventure A/S, Denmark) equipped with a double-sided MagVenture Cool-B65 coil. A Localite neuronavigation system (Localite GmbH, Sankt Augustin, Germany) will be used to position the TMS coil over the individualized stimulation target at each session. All participants will receive stimulation using iTBS over the LDLPFC (1800 pulses per session). The individualized treatment targets will be produced from structural and functional MRI scans using the software services of Magnus Medical. The targeting approach will be the same as that used in prior publications (Cole et al., 2020, 2022; Williams et al., 2018).

Stimulation intensity will be standardized at 90% of left RMT, adjusted to skull to cortex distance. No further adjustments are needed based on other patient characteristics or conditions. For safety, stimulation will never be delivered above 120% rMT. Sessions will be delivered using the MagVenture MagPro X100 stimulator, with triple-pulse 50-Hz bursts given every 200ms (at 5 Hz).

The iTBS protocol will consist of a 2s train of bursts given every 10 s for a total of 570s (1800 pulses) over the LDLPFC.

If treatment emergent mania occurs (defined as an increase of 2 or more points in at least 2 YMRS items or clinician judgment), we will discontinue treatment and adjust anti-manic medication and, if necessary, add on other pharmacologic measures (neuroleptics, benzodiazepines) as clinically indicated with the intent to treat until remission is achieved.

Neuroimaging Biomarkers:
We will perform structural and resting state functional connectivity MRI with a 3T system prior to active study phase and immediately after active study phase (up to 5 days following final iTBS stimulation). The MRI scans will require about 1 hour in the MRI scanner. During the scan, participants will lie on the table in the magnet while the images are acquired. Instructions may be given through an auditory system. Subjects will wear earplugs and may be fitted for a bite bar to help them to keep their head still during the scans; for studies that enroll older adults, a bite bar will not be used so as to accommodate participants with dentures. These procedures have been used previously in younger and older adults alike, and do not cause undue distress in subjects.

At Baseline and 1 week, our MRI scans will include:
-Anatomical (T1) - 5min
-Resting state fMRI - 24 min
-Resting state ASL - 7 min

-Diffusion-weighted imaging (DWI) - DWI acquisition will take approximately 4 min along 90 non-collinear directions with a b-value=2400s/mm2.
TOTAL scan time: ~40min

Biomarker measures: We will use a canonical hemodynamic response function (HRF) convolved event-related model with temporal and dispersion derivatives to model the blood oxygen level dependent (BOLD) in the context of a generalized linear model. Separate regressors (convolved with the HRF) will be created for stimulus events in each paradigm. Temporal and dispersion derivatives will be treated as regressors of no interest. A region of interest (ROI) analysis will be performed using our established methods, to identify BOLD-dependent signal change in the dorsolateral prefrontal cortex, subgenual cingulate, and default mode network nodes (right, left). Beta values for each ROI will be extracted for each subject for regression analyses.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Screening (Day -50 to Day -5)	Baseline (Day 0)	Active Study (Day 1)	Active Study (Day 2)	Active Study (Day 3)	Active Study (Day 4)	Active Study (Day 5)	Follow up: Immediate (Day 8 to Day 10)	Follow up: 1-month (Day 30 to Day 40)
Informed Consent	X								
Medical History/Records	X								
MRI Safety Form	X								
Structured Clinical Interview	X								
Clinician Administered Scales	X	X	X	X	X	X	X	X	X
Self-Rated Scales	X	X	X	X	X	X	X	X	X
Biometric Data		X	X	X	X	X	X	X	X
MRI		X						X	
Neurocognitive Measures		X						X	
Study Treatment			X	X	X	X	X		
Continue Medications	X	X	X	X	X	X	X	X	X
Monitor for Adverse Events			X	X	X	X	X		

6.2 Descriptions of Evaluations

Screening [Day -5/-50]:
We will recruit participants from our clinics with a treatment history verifying they meet inclusion/exclusion criteria (see below in Section 5). We will obtain informed consent from the participant and a trained rater will administer a SCID (Structured Clinical Interview for DSM-5) to confirm the diagnosis of bipolar I disorder. Participants will be staged using a modified Maudsley staging method tailored for bipolar depression to determine the severity of treatment resistance. The consenting and clinical screening assessment will be preformed in-person, or virtually by secure audio/video platform as works best for the individual and current COVID environment. We will also gather the participants' medical records and review all information to screen for inclusion and exclusion criteria, MRI safety, TMS safety, medical and psychiatric history, a pregnancy test, and current medications.

At the clinical screening assessment, a trained rater will also collect the following assessments:

1. MADRS (Montgomery-Asberg Depression Rating Scale)
2. YMRS (Young Mania Rating Scale)
3. CGI-BP (Clinical Global Impression – Bipolar Disorder)
4. ATHF current and lifetime (Antidepressant Treatment History Form) – ATHF reviews patient antidepressant trials to assess whether patients have had "failed, adequate trials" of various classes of antidepressants.
5. TASS (Transcranial Magnetic Simulation Adult Safety Screen) – a screening form that evaluates prior adverse reaction to TMS and various seizure risk factors and relative contraindications

Participants will also complete the following:

1. AS-18 (Affective Self Rating Scale)
2. PANAS (Positive and Negative Affect Schedule)
3. digiBP (Digital Self-Report Survey of Mood for Bipolar Disorder)
4. MADRS-S (Montgomery-Asberg Depression Rating Scale – Self Rated)
5. C-SSRS (Columbia Suicide Severity Rating Scale)

Baseline [Day 0]:
Baseline visits will be separate from screening visits to confirm stability of symptoms. Participants will have an MRI scan in the morning (see Neuroimaging Biomarker section below for more details).

Baseline clinical measures will include:

1. MADRS
2. YMRS
3. CGI-BP

Baseline self-report measures will include:

1. AS-18
2. PANAS
3. digiBP
4. MADRS-S
5. C-SSRS

Cognitive measures collected using Cambridge Neuropsychological Test Automated Battery (CANTAB) software on a tablet. Neurocognitive Measures will include:

1. Rapid Visual Information Processing (7 min): sensitive tool for assessment of sustained attention
2. Delayed Matching to Sample (7 min): test of attention and recognition.
3. One Touch Stocking of Cambridge (10 min): test of executive function, planning and working memory based upon “Tower of Hanoi”.
4. Stop Signal Task (20 min): test of impulse control and response inhibition.
5. Cambridge Gambling Task (18 min): test of decision making and risk-taking behavior outside a learning context.
6. Emotional Bias Task (Happy-Sad) (4 min): detects perceptual bias in facial emotion perception.
7. Emotional Recognition Task (6 min): measures the ability to identify six basic emotions from facial expressions
8. Multi-Tasking Test (8 min): assesses ability to manage conflicting information and ignore task-irrelevant information

Biometric data will be recorded daily by a wearable device that captures biometric data provided by Magnus Medical. This device will be worn daily from baseline through follow-up. Biometric data measures include:

1. Heart Rate Variability
2. Actigraphy
3. Body Temperature
4. Sweat Chloride

Active Study [Day 1-5]:
TMS sessions will be scheduled in a 5-day sequence, resulting in a total of up to 50 sessions. Prior to each daily treatment series, participants will be asked a short series of

questions assessing medication compliance and substance use, amount and quality of sleep, and any other changes in mood since their last treatment session. We will monitor any medication changes throughout the course of the entire study. Participants will receive up to 10 daily stimulations with active iTBS over the left dorsolateral prefrontal cortex (LDLPFC) (1800 pulses). In the event of depression treatment remission (i.e. MADRS </=10), treatment emergent mania occurring (defined as an increase of 2 or more points in at least 2 YMRS items), or clinician judgment, LDLPFC treatment will be discontinued and emergent symptoms will be treated by increasing the dose of the participant's anti-manic agent and other pharmacologic measures if necessary as assessed by the onsite clinician.

If participants do not experience a significant increase in manic/hypomanic symptoms (>/=2 item increase of 2 or more points on the YMRS scale), LDLPFC treatment will continue until MADRS </=10 or the end of the 5-day treatment series is reached.

Each session will be separated by a 50-minute break. This separation between stimulation sessions decreases the risk of associated TMS side effects (e.g. irritation from the device, headache). The modified PANAS (items 3, 9, 11, 17, 18, 19) will be administered between every stimulation session to assess for any potential shift towards (hypo)mania. If a significant increase (>/=2 item increase of 2 or more points) is observed, the YMRS will be administered.

Active study clinical measures collected at beginning and end of each treatment day (unless where noted) will include:

1. YMRS (AM and PM)
2. MADRS (AM, PM, and as clinically indicated)
3. Daily Check-In Form (AM only)

Active study self-report measures collected at end of each treatment day will include:

1. AS-18
2. digiBP
3. MADRS-S

The goal will be to treat participants to remission over the course of 5 days or earlier (when patient achieves remission of symptoms per MADRS </=10).

Follow-up [Day 8-40]:
Due to COVID-19 or related considerations, we will perform follow-up assessments via a secure audio/video platform in cases where we cannot conduct in-person assessments or per participant preference.

For participants completing treatment prior to the 5-day period, immediate post-treatment evaluation is defined as up to 5 days after the last day of treatment and 1-month post-treatment evaluation is defined as 25-35 days after the last day of treatment.

Participants will have the same clinical and neurocognitive assessments that were completed during the baseline time-period at the immediate post-treatment and 1-month post-treatment mark. In addition, we will also administer the CGI-BP at these 2 time points.

Participants will complete the following self-report assessments at these two follow-up time points as long as they meet responder/remission criteria:

1. AS-18
2. PANAS
3. digiBP
4. MADRS-S
5. C-SSRS

If participants do not remit but respond (>/=50% decrease on the MADRS from baseline) to treatment by the end of the acute, 5-day treatment series, they may be referred to a TMS clinic or further treatment per their outpatient psychiatrist.

6.3 Description of Study Measures

a. Montgomery-Asberg Depression Scale-Clinician Rated (MADRS): The MADRS is a ten-item clinician rated questionnaire. Total scores can range from 0 to 60, with higher scores indicating greater severity of depression (0-6 normal range, 7-19 mild depression, 20-34 moderate depression, >34 severe depression). We will utilize this assessment to determine participant's level of depression and consequent eligibility for the trial. We will then subsequent utilize the MADRS daily and at follow up as our primary outcome measure.

b. Young Mania Rating Scale (YMRS): The YMRS is an 11-item clinician-administered scale used to measure symptoms of mania. Each item is scored from 0-4 with scores of 4 indicating the presence of more severe mania. This scale will be used to monitor symptoms of mania through each day of iTBS treatment.

c. Clinical Global Impression Scale - Bipolar Disorder (CGI-BP): The CGI-BP is a 3-item clinician rated scale to provide a global rating of severity of manic and depressive

episodes and the degree of change from the immediately preceding phase and from the worst phase of illness. Each item is rated from 1 to 7 (0 = not assessed and 7 = very much worse or severely ill). The CGI-BP will be administered at screening, baseline and visit follow ups for a more global assessment of patient's illness and symptoms.

d. Affective Self Rating Scale (AS-18): The AS-18 is a 18 item self-rating scale that assess depressive, manic, and mixed affective states. Each symptom is rated from 0 "none" to 4 "very severe". The AS-18 will be filled out at every study encounter: screening, baseline, active study, and follow up.

e. Positive and Negative Affect Schedule (PANAS): The PANAS is a 20-item self report scale that consists of different words that describe different positive and negative feelings and emotions. Every item is rated from 1 "very slightly or not at all" to 5 "extremely". The PANAS will be filled out screening, baseline, and follow up encounters. A modified PANAS (items 3, 9, 11, 17, 18, 19) will be administered between every stimulation session to assess for any potential shift towards (hypo)mania

f. Digital Self-Report Survey of Mood for Bipolar Disorder (digiBP): The digiBP is a 6-item digital survey for measuring mood in bipolar disorder. It has three depressive items (depressed mood, fidgeting, fatigue), two manic items (increased energy, rapid speech), and one mixed item (irritability); and recovers two scores (m and d) to measure manic and depressive severity. The digiBP will be filled out at every study encounter: screening, baseline, active study, and follow up.

g. Montgomery-Asberg Depression Scale-Self Report (MADRS-S): The MADRS-S is the self-report version of the original ten-item clinician rated questionnaire (MADRS). The MADRS-S comprises 9 items rated on a 0-3 point scale which are summed to calculate a total score. This score is then doubled for comparison with the clinician version of the MADRS. The MADRS-S will be filled out at every study encounter: screening, baseline, active study, and follow up.

h. Columbia Suicide Severity Rating Scale (C-SSRS): The C-SSRS is questionnaire used for suicide assessment. The C-SSRS measures four constructs: the severity of ideation, the intensity of ideation, behavior and lethality. It includes "stem questions," which if endorsed, prompt additional follow-up questions to obtain more information. We will utilize this along with clinical assessment to monitor for participant's suicide risk. The C-SSRS will be filled out at screening, baseline and follow up.

7. SAFETY ASSESSMENTS

Risk Assessment:

TMS: Extensive published data show that this accelerated theta-burst rTMS protocol in prefrontal cortex is safe and very well tolerated (Sonmez et al., 2019). The most common side effects were mild headache, fatigue, and some discomfort at the stimulation site.

No seizures were observed in any of the above studies. However, very rarely, TMS can induce seizures (17 reported cases to date among tens of thousands of participants treated with rTMS, but few to none if proper safety and enrollment procedures are followed), with a seizure risk at approximately 1:30,000 sessions for traditional high frequency rTMS (Rossi et al., 2009). To minimize the chances of this adverse event, participants with seizure history will be excluded. The FDA has considered studies of standard TMS to be nonsignificant risk (not requiring an IDE).

Another potential immediate risk is that of induction of mania. Although there have been no such cases of mania induced by TBS, there have been at least 13 cases of rTMS-induced mania reported from fixed-frequency rTMS in participants with depression (Xia et al., 2008). The rTMS-induced mania rate reported by Xia et al was 0.84% as compared to 0.73% for sham, which were not significantly different from each other.

Another potential risk is mild pain at the site of stimulation, which occurs during stimulation only, and which wanes with each session. There is also a risk of psychological distress related to this pain, should it occur, though discomfort associated with rTMS is typically mild, and not distressing when participants are reassured it is not dangerous. For participants that continue to experience discomfort with TMS, pre-treatment with acetaminophen, ibuprofen, and/or lidocaine will be allowed as warranted. Participants and treaters will wear earplugs during all treatment sessions. In between sessions, participants will be placed in a relaxing environment to maximize psychological well-being.

MRI: Common MRI risks include claustrophobia, localized twitching (not painful) sensation during MRI, and tinnitus after MRI. There are some contraindications that may prevent a participant from having a scan; however, all participants will be screened prior to scanning to evaluate these risk factors. Due to the strength of the magnetic field, contraindications include participants with heart pacemakers, metallic foreign bodies in their eye, and brain aneurysm clips, as the magnetic field may dislodge the metal leading to injury.

Confidentiality: A risk of all clinical studies is that they collect personal information that may be seen by individuals not associated with the study. This could lead to psychological, social, and cultural risks. However, we will use best practice procedures to minimize the potential for breaches of confidentiality. To protect participants' confidentiality, a numerical system will be used as unique identifiers, and identifying information will not be stored with the data. Electronic data will be collected via REDCap, a HIPAA compliant electronic data capture system, maintained in a protected environment in the SAFE Desktop Environment at Johns Hopkins. Secured information linking participant's ID with protected health information will be separated from the unidentified data. All treatment interactions will occur in a closed-door room with specified study personnel. We will have private rooms available for all participant interviews and follow-up interactions. All video meetings will be conducted using the PHI-safe Zoom video meeting interface or comparable platform.

Long-range Risks: No long-range risks associated with TBS or routine MRI have been reported, and none are anticipated for this study.

Potential Benefits:
Participants may have reduction and/or remission of depressive symptoms allowing for improved quality of life, engagement, and functioning. This translates to other downstream benefits such as increased societal/economic productivity. Further, this study may give a way for participants to receive rTMS treatment who otherwise would be ineligible given that rTMS treatment is not covered by many insurance carriers. Demonstration of SAINT efficacy may lead to larger real-world clinical trials for both bipolar I disorder but also perhaps other psychiatric conditions.

7.1 Methods for Assessing Adverse Events

Seizure: A physician will be available at all times during treatment to evaluate any participant experiencing a suspected seizure.

Mania: The rTMS parameters used in this study are the least risky because the intervals of stimulation have been shown to be appropriate for theta burst stimulation in the motor system with no adverse outcomes. Moreover, participants' symptoms will be monitored carefully by both members of the research team and clinical staff. The YMRS will be administered daily to check for mania symptoms. If the participant displays an increased YMRS score (>/=2 points) on 2 questions, stimulation will be stopped and patient will be treated for emergent symptoms via increase of their anti-manic agent and other pharmacologic measures as indicated per clinician assessment.

If any of the research team or clinical staff believe that the participant may be showing signs of hypomania/mania, the YMRS will be administered by trained personnel immediately, the researchers will not wait until the daily assessments are conducted. Further, independently, the modified PANAS (items 3, 9, 11, 17, 18, 19) may be administered between every stimulation session to assess for any potential shift towards (hypo)mania. If a significant increase (>/=2 item increase of 2 or more points) is observed, the YMRS will be administered.

Suicide: Monitoring participants depressive symptoms will allow the identification of individuals at risk of suicide and therefore the risk of this occurring can be minimized. At screening, baseline, and follow up the C-SSRS will be administered to directly assess suicidal risk. During active study days suicide risk will be screened via the MADRS which has a question to assess suicidal thoughts. Evaluation of the suicidal risk assessments will be made by the research team immediately upon collection of these insturments to determine if any follow-up is needed as described in section 7.2.

7.2 Management of Adverse Events

Seizure: In the unlikely occurrence of a suspected seizure, participation will be discontinued and the participants will be provided with a referral to outpatient care. Any seizure that theoretically could occur would likely be self-limited and lead to no residual neurological impairment. Seizures induced by rTMS are rare, brief and don't result in sequelae, with no events of status epilepticus ever being reported (Rossi et al., 2009).

Mania: In the event of emergent mania symptoms (defined as an increase of 2 or more points in at least 2 YMRS items), or clinician judgment, treatment will be discontinued and emergent symptoms will be treated by increasing the dose of the participant's anti-manic agent and other pharmacologic measures if necessary as assessed by the onsite clinician.

Suicide: If any study personnel believe a participant is at suicide risk, the site PI will be notified immediately and an emergency consultation between them, clinical staff, and the participant will be had. If the study team considers it necessary, the patient will be referred for emergency psychiatric treatment.

7.3 Reporting Procedures

All adverse events occurring in this study will be reported to both local and Central IRBs according to each institutions' IRB policies. Central IRB shall promptly notify the Principal Investigators (PI) of the study as designated on the IRB protocol submission of all IRB decisions and shall make available to the PIs all applicable study related documents

including but not limited to approved protocols, consent forms, surveys, and decision letters.

All adverse events will also be reported to Magnus Medical, who manufacture the TMS device intended for use in this study, via their safety email address (safety@magnusmed.com).

7.4 Follow up for Adverse Events

All adverse events will be followed through until the event(s) have resolved, no further action is required, or participant has been transferred to an appropriate level of clinical care. The study team will communicate with the participants' pre-study care team to coordinate care.

8. INTERVENTION DISCONTINUATION

Participants are free to withdraw from the study at any time for any reason. Study doctors are to discontinue participants from the study if participants:

- Request early discontinuation or withdraw consent.
- Experience a serious or intolerable adverse event that prevents the participant from continuing.
- In the Investigator's opinion, is experiencing a clinically significant deterioration.
- Conduct a protocol violation, including lack of compliance.
- Are "lost to follow-up" as defined as no response from participant after daily attempts to contact over the planned five day treatment course.
- Encounter other conditions (such as administrative issues or pregnancy).

If a participant discontinues from the study at any time at their own request or at the study clinician's discretion, the reason(s) for discontinuation are to be recorded by the study.

Participants are to continue care with their pre-study care team. If participants do not remit but respond (>/=50% decrease on the MADRS from baseline) to treatment by the end of the acute, 5-day treatment series, they may be referred to a TMS clinic. If participants are withdrawn from the study for reasons related to the treatment (typically adverse event within 30 days of last treatment), they will be followed until the event(s) have resolved or no further action is required. The study team will communicate with the participants' pre-study care team to coordinate care.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Considerations

This is an open label pilot study. The study will not include blinding given that this is a single group assignment to treatment. Study will not include a placebo or non-treatment group as this is a feasibility pilot study.

The sample size for this pilot study was selected to allow for a sufficient evaluation of the feasibility of carrying out the protocol across multiple NNDC centers given the available resources and provide preliminary data to motivate further study of this treatment approach.

9.2 Early Stopping Rules

The study will be terminated if:

Three or more participants reach hypomania as defined by a score of greater than 10 on the YMRS scale without resolution (YMRS <10) within 24 hours with pharmacologic measures as outlined above.

9.3 Outcomes

9.3.1 Primary Outcome

The primary outcome measures for this study will be change in MADRS scores. The MADRS is a clinical assessment tool used to rate a patient's level of depression and is the standard scale used for depression research studies. The YMRS will be used as a second primary outcome measure to assess any changes in symptoms of mania over the course of treatment. The YMRS is a clinical assessment tool used to assess the presence and severity of manic symptoms. The primary outcome measures will be assessed as the change between baseline and immediate (up to 5 days after last day of treatment) post-treatment assessment.

9.3.2 Secondary Outcomes

Secondary outcome measures will include changes in MRI derived functional connectivity of the subcallosal cingulate to the DLPFC and within the default mode network. Secondary outcome measures will be assessed as the change between baseline and 1-month post-treatment assessment. Exploratory endpoints include biometrics related to sympathetic nervous system activity - Heart Rate, Sweat Chloride, Body Temperature, and Actigraphy.

9.4 Data Analyses

The primary outcome measures will be analyzed using generalized linear mixed models to test if there are significant changes in scores over follow-up. Based on previous work, we will use a compound symmetry or autoregressive covariance structure (based on distribution of residuals) and robust estimation of coefficients to handle violations of model assumptions. Random effects will be included to account for repeated measures on the same participants, and fixed effects of time will be evaluated controlling for fixed effects of age, sex and number of days to reach treatment remission. All post hoc pairwise comparisons will be Bonferroni corrected. Exploratory endpoints related to biometrics will be analyzed in similar fashion.

For assessment of the secondary outcome measures of change in functional connectivity, we will employ a resting-state seed-based functional connectivity approach to assess connectivity between the subcallosal cingulate connectivity to the DLPFC and within the default mode network. For each participant, the correlation coefficients between average blood oxygen level-dependent (BOLD) time series of the seed-region and the BOLD time series of each grey matter voxel within the DLPFC or default mode network will be calculated. The correlation coefficient will be converted to normally distributed z scores by the application of Fisher's r to z transformation. The resulting connectivity maps will be analyzed with repeated measures ANOVA to compare pre-iTBS vs post-iTBS connectivity measures as a within-subject variable, and sex and site as a between-subject covariate.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. Clinical study staff will oversee the collection and organization of study data, and the investigator will ensure the accuracy, completeness, legibility, and timeliness of the data reported. The study will not include blinding given that this is a single group assignment to treatment.

10.2 Data Management

Study data will be collected and managed with REDCap, a secure online data capture system, maintained at the Johns Hopkins University site, which will serve as the Data Coordinating Center for the study. Participant information will be coded in REDCap with an anonymous study ID assigned by the REDCap system. Personally identifiable information will not be kept in the REDCap database. Local sites will be responsible for maintaining personally identifiable information and link to the anonymous study ID for the participants recruited at their sites. The clinician and patient rated assessments will be built into the REDCap database. We note that all assessments described above are well validated and widely used measures. Copies of each of the assessments are included as attachments.

10.3 Quality Assurance

10.3.1 Training

Clinical study staff will undergo or have already undergone training requisite for administration of TMS as well as study clinical measures by

10.3.2 Protocol Deviations

Unanticipated problems or study deviations will be reported to the IRB within 10 days of the PI becoming aware of such problems or deviations in accordance with the IRB policy on prompt reporting.

10.3.3 Monitoring

Study team will meet to discuss potential participants after screening and record review to ensure they meet inclusion/exclusion criteria and are appropriate for this study. Study team will have monthly meetings to review and ensure protocol compliance as participant’s are enrolled and undergo active study treatment.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the study. The consent form should be separate from the protocol document.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's record.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must be approved by Central IRB prior to use. The ICF will adhere to Central IRB requirements, applicable laws and regulations.

11.3 Participant Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept on secure servers. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB.

13. Outline of JHU Roles and Responsibilities

13.1 Coordinating Center

JHU will serve as the Coordinating Center for this study. PI has contact information for all sites. Each participating center has on file an active FWA with OHRP. Any protocol updates will be sent to each participating site PI with comments regarding changes. All protocol events and deviations will first be simultaneously reported to both site PI and lead PI. Apart from this, monthly meetings will be held to discuss protocol events and deviations to ensure appropriate reporting to the JHM IRB. All data will be stored on JHU REDCap and SAFE Desktop. PI will ensure data collection after each participant.

13.2 Single IRB

Johns Hopkins Medicine is serving as the single IRB for this study. It is the preference of Johns Hopkins Medicine IRB to use the SMART IRB reliance agreement as the basis of reliance. The SMART IRB master reliance agreement was created in 2016 to harmonize and streamline the IRB review process for multisite studies. It enables reliance on a study-by-study basis, clearly defines roles and responsibilities of relying institutions and reviewing IRBs, and eliminates the need to sign reliance agreements for each study [e.g., a non-SMART IRB agreement]. 900+ institutions have already signed onto this agreement and are actively using it as the basis of reliance for multisite projects. Sites that will rely on JHM IRB are still responsible for conducting a local context review prior to the start of research at their site and for following any local and institutionally required policies as it applies to research at their site [e.g., reporting of unanticipated problems].

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