CLINICAL RESEARCH PROTOCOL

INVESTIGATIONAL PRODUCT(S):		[MagPro X100 Stimulator, Cool-B65 Butterfly Coil. A form of transcranial magnetic stimulation to be used with patients with depressive symptoms.]
STUDY NUMBER(S):	**IRB Number**	[850359]
	Other Protocol Identifiers	[N/A currently]
PROTOCOL(S) TITLE:		[Intensive TMS for Rapid Relief of Bipolar Depression Symptoms]
IND NUMBER:		[N/A]
SPONSOR-INVESTIGATOR:		[Dr. Yvette Sheline, MD]
FUNDING SPONSOR(S):		[Milken Institute]
PRINCIPAL INVESTIGATOR:		[Dr. Yvette Sheline, MD as PI Dr. Claudia Baldassano, MD Dr. Michael Thase, MD]
ORIGINAL PROTOCOL DATE:		[N/A]
VERSION NUMBER:		[V1.2]
VERSION DATE:		[20 September 2022]

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PRINCIPAL INVESTIGATOR SIGNATURE

STUDY FUNDING SPONSOR:	[Milken Institute]
STUDY TITLE:	[Intensive TMS for Rapid Relief of Bipolar Depression Symptoms]
STUDY ID	[850359]
PROTOCOL VERSION	[V1.3]

I have read the referenced protocol. I agree to conduct the study in accordance to this protocol, in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

Principal Investigator Name	Yvette Sheline	Signature	
Affiliation:	University of Pennsylvania	Date	9/20/2022

Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
MP	Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat

LSMEANS	Least-Squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
DSMC	Data Safety Monitoring Committee
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
UP	Unanticipated Problem
US	United States

1 STUDY SUMMARY

1.1 Synopsis

Title:	[Intensive TMS for Rapid Relief of Bipolar Depression Symptoms]
Short Title:	[Intensive TMS for Bipolar Depression]
Study Description:	[The research study is being conducted to test whether using high dose spaced theta-burst rTMS (a form of transcranial magnetic stimulation) produces a significant reduction in depressive symptoms compared with sham. This project will recruit patients aged 18-70 with symptoms of bipolar depression who have failed (or not shown signs of improvement) after at least two prior treatments. The null hypothesis is that there will be no difference in reductions in depressive symptoms by the end of a five-day treatment period. The alternative hypothesis is that, compared with sham, active TMS will result in a greater reduction in depressive symptoms by the end of the treatment period.]
Objectives:	[The overall objective of this project is to test whether using high dose spaced theta-burst rTMS (HDS-TBS) produces a significant reduction in depressive symptoms compared with sham.]
Primary Endpoint:	[Aim 1: To assess clinical efficacy of HDS-TBS.]
Secondary Endpoints:	[Aim 2: To determine the effect of iTBS on DLPFC rsfMRI and establish a relationship between change in brain resting state functional connectivity and treatment effects.]
Study Population:	[34 subjects (with 32 usable data), within the ages of 18-70, right or left handed, gender inclusive, diagnosed with Bipolar I & II depressed (per DSM 5 criteria)]
Phase:	[N/A]
Description of Sites/Facilities	[Center of Neuromodulation in Depression & Stress, University of Pennsylvania]

Enrolling Sites: [Center of Neuromodulation in Depression & Stress, University of Pennsylvania]

Description of Study Intervention: [Intensive iTBS. This includes intermittent theta-burst stimulation (iTBS), a patterned form of repetitive transcranial magnetic stimulation (rTMS) over the left dorsal lateral prefrontal cortex (L-DLPFC).]

Study Duration: [1 year]

Participant Duration: [6-8 weeks]

1.2 Key Roles and Study Governance

Funding Sponsor	*Principal Investigator/Sponsor-Investigator*
Milken Institute	*Dr. Yvette Sheline, MD*
Milken Institute	*University of Pennsylvania*
Santa Monica Office *1250 Fourth Street* *Santa Monica, CA 90401*	*3700 Hamilton Walk Richards 307* *Philadelphia PA 19104-6019*
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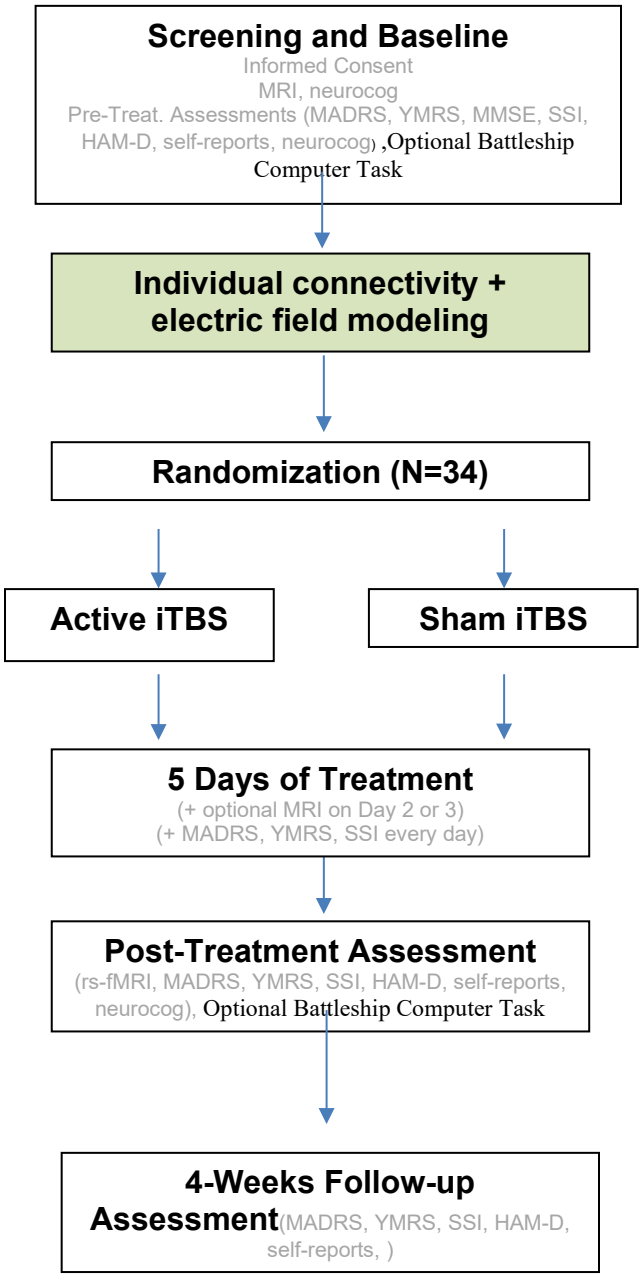
inquiries@milkeninstitute.org *;* *bipolargrant@milkeninstitute.org*	*sheline@pennmedicine.upenn.edu*

1.3 Schema


Screening and Baseline
Informed Consent
MRI, neurocog
Pre-Treat. Assessments (MADRS, YMRS, MMSE, SSI, HAM-D, self-reports, neurocog) ,Optional Battleship Computer Task
Individual connectivity + electric field modeling
Randomization (N=34)
Active iTBS
Sham iTBS
5 Days of Treatment
(+ optional MRI on Day 2 or 3)
(+ MADRS, YMRS, SSI every day)
Post-Treatment Assessment
(rs-fMRI, MADRS, YMRS, SSI, HAM-D, self-reports, neurocog), Optional Battleship Computer Task
4-Weeks Follow-up Assessment(MADRS, YMRS, SSI, HAM-D, self-reports,)

2 INTRODUCTION AND RATIONALE

2.1 Study Rationale

[Bipolar disorder (BD) is prevalent, severe and under studied, and is often excluded from clinical trials. The depressive phase of illness accounts for the majority of time ill: 72% in BD-I and 81% in BD-II [1]. Many patients fail to respond adequately or cannot tolerate pharmacotherapy due to side effects. Thus alternative treatment options are important to help achieve and sustain remission.

One option, transcranial magnetic stimulation, (TMS) is a relatively new non-invasive approach that involves modulating brain networks with magnetic pulses applied to the skull surface. To date, the best evidence for TMS efficacy has been demonstrated in treatment resistant major depression, although there have been a small number of studies finding treatment response in BD [2] High dose spaced theta burst TMS (HDS-TBS) is among recent emerging technologies for rapid reduction of depressive symptoms.]

2.2 Background

[Li et al [3]first described the efficacy of a course of intermittent theta-burst stimulation (iTBS), a patterned form of repetitive transcranial magnetic stimulation (rTMS) over the left dorsal lateral prefrontal cortex (L-DLPFC) in patients with treatment refractory depression. In that study the degree of refractoriness was predictive of reduced efficacy, suggesting that highly refractory patients may require more TMS pulses to produce an antidepressant response. TBS has been shown to be more efficient than standard rTMS in modulating cortical excitability and multiple spaced iTBS (intermittent theta burst stimulation) sessions can be used to accelerate the treatment response. Recent work with transcranial magnetic stimulation (TMS) has shown that a rapid and sustained treatment response can be achieved by concentrating the usual 4-6 weeks of daily treatment into a high dose spaced theta burst TMS (HDS-TBS) treatment for 5 days [4]. Patients in that study were required to have failed conventional rTMS treatment and to meet deep brain stimulation inclusion criteria. However, that study only included MDD and excluded bipolar disorder. To date, there are no studies of HDS-TBS in bipolar disorder.

To demonstrate the feasibility of administering a high dose TBS protocol in our Center we recruited six patients with MDD into a pilot study using HDS-TBS according to the same parameters as will be used in the current proposal (10 treatments/day x 5 days), with the same stimulation settings. In our pilot study (IRB Protocol #834723), however, we only included participants with a diagnosis of MDD. Following treatment, patients had a mean reduction of 38.6% in depressive symptoms on the MADRS.]

2.2.1 Pharmacokinetics, Pharmacodynamics and Toxicology

[N/A]

2.2.2 Assessment for Potential Study Products Drug-Drug, Drug-Device, Device-Device Interactions

[No other drugs or devices are included in this trial, besides the TMS system.]

2.2.3 Clinical Adverse Event Profile

[Common mild AEs from TMS include: headache, local pain and discomfort, dizziness/nausea. Rare severe AEs from TMS include: seizures, worsening of depression, hearing loss, burns form the coil.

Other AEs include emotional discomfort during assessments, physical discomfort with MRI, anxiety or claustrophobia during MRI, worsening of depressive symptoms over time, mania symptoms and suicidality. In rare instances, severe AEs from MRI can include injury.]

2.2.4 Dosing Rationale

[MagVenture TMS Therapy System with Theta Burst Stimulation is FDA approved.]

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

[**iTBS &TMS.** This study utilizes two forms of Transcranial Magnetic Stimulation (TMS): intermittent Theta Burst Stimulation (iTBS) & single pulse TMS. TMS is a FDA-approved non-invasive brain stimulation technique for a variety of diagnoses. iTBS was recently approved by the FDA to be used to treat depression as well. As with any technique, there may be long-term risks due to TMS that are currently unknown. The most common side effect of TMS (approximately 25% of subject) is a mild headache. There are no known long-term adverse effects reported with the use of this device. Rarely, device malfunction could result in a scalp burn (less than 1% of subjects).

- **Certain Medical Diagnoses**: For subjects with epilepsy, activation of the brain by TMS could also activate a seizure. Subjects with stroke may be at increased risk for a seizure due to the brain scar, therefore, those with history of epilepsy or stroke will be excluded from the study. For a typical physically healthy person, a TMS-induced seizure in this experiment is very unlikely.
- **Noise**: The TMS device produces a clicking sound. To minimize this possibility, you will be given protective earplugs or headphones.
- **Nausea**: Although it is uncommon, approximately 5% of subjects have experienced nausea during the experiment. You can discontinue the experiment if you experience any discomfort during the study.
- **Mild Swelling or Bruising**: You may also experience temporary and local bruising, swelling, or pain from the swim cap and/or muscle activation by TMS.

Accelerated iTBS. Present research about increased iTBS frequency [3, 4] does not suggest any increased risk of side effects due to the increased treatment frequency. Current research also showed no significant difference between accelerated and conventional TMS treatment schedules [5] That being said, patients will be monitored for worsening of depressive symptoms or side effects. If patients experience worsening of depressive symptoms (i.e. increased insomnia, increased negative thoughts, increased suicidality), they will be referred to the study physician and/or to research study staff for evaluation and possible next steps.

Clinical assessments and self-report questionnaires. Some discomfort may be associated with the clinical assessments conducted in this study. Patients may experience emotional discomfort when answering some questions in the questionnaires or when talking about personal information. They may choose not to answer any of the questions and to terminate study participation.

MRI Scan.

- **Claustrophobia**: Patients may experience claustrophobia (fear of enclosed spaces and/or anxious feelings accompanied by fast heart rate or shortness of breath) within the MRI scanner. An MRI scan requires participants to be in a partially enclosed space inside the scanner. Some people may find this to be uncomfortable and claustrophobic. Patients need to inform the doctor ordering the scan, or the study staff, if they suffer from claustrophobia.
- **Magnetic Fields**: There is no known health risk associated with exposure to magnetic fields during an MRI. There are minimal risks from the loud noise associated with the MRI scanner and from the discomfort of lying on a hard surface. We shall provide protective earplugs as necessary and make every attempt to ensure comfort with blankets, etc. during time in the scanner.
- **Flying Objects**: The greatest risk of MRI is a magnetic object flying through the air toward the magnet and hitting you. To reduce this risk we require that all people involved with the study remove all magnetic metal from their clothing and all magnetic metal objects from their pockets. No magnetic metal objects are allowed to be brought into the magnet room at any time except by approved personnel. In addition, once in the magnet, the door to the room will be closed so that no one inadvertently walks into the room.
- **Medical Implants and Foreign Bodies**: There is also a potential risk of MRI for subjects with medical implants or other metallic objects in their body. All subjects undergoing MRI scanning must complete a screening evaluation risk in advance of the study for the presence of medical implants or other foreign bodies that could pose an injury. Every effort will be made to insure that disclosed implants or foreign bodies do not pose a risk to subjects. In cases where there is insufficient information to evaluate the risks associated with an implant or foreign body, the MRI study will not be allowed to proceed.

- **Pregnancy**: Although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no possible benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women.
- **Incidental Findings Clause**: This MRI is not a clinical scan. It is possible that during the course of the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform patients if necessary. These possible finding(s) may or may not be significant and may lead to anxiety about their condition and to further work-up by outside physician.

Worsening of Depression Symptoms. While participating in this study, symptoms worsen to the point where of needing psychological or medical support, patients will be given resources to emergency services. If a patient's symptoms require urgent attention, they will be informed to call 911 and present to the nearest emergency room or contact: Philadelphia Behavioral Health at (215) 686-4420. PBH hotlines are staffed 24 hours a day, 7 days per week. For similar hotlines outside of the Philadelphia area, they can consult www.suicide.org.

Risk to confidentiality. There is a rare risk that confidentiality could be breached in this study. Breaches in confidentiality could impact future insurability and/or employability.

Dr. Thase will provide clinical monitoring as needed. He will act as clinical and safety monitor and ensure compliance.]

2.3.2 Known Potential Benefits

[There may not be any direct benefit to all patients. However, given the clinical data, it is likely that many participants may receive a reduction of symptoms.]

2.3.3 Assessment of Potential Risks and Benefits

[The risks associated with this study are no greater than those encountered in standard clinical treatment with Transcranial Magnetic Stimulation (TMS). The aspects of this study that are implemented for the purposes of the study alone (the MRI scan and assessments of symptoms) are minimal risk. Participants who have an obvious contraindication to TMS or MRI in their medical record will not be presented in this study; those who consent will be asked to complete an MR-safety form upon consent. Should any MRI contraindications be discovered at this time, they will not be enrolled in the study.

The potential benefit to patients (e.g., reduced time burden) and medical community through the increased understanding of this treatment method for individuals with depression, far outweighs the potential risk from the MRI and TMS procedures.]

3 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	*ENDPOINTS*	*JUSTIFICATION FOR ENDPOINTS*
Primary		
The primary objective is to assess clinical efficacy of HDS-TBS.	*The primary outcome will be response to TMS treatment as evidenced by change in the Montgomery Asberg Depression from the pre-treatment baseline to the end of the 5-day treatment course.*	*We have used the MADRS in many prior studies. The MADRS will be the primary outcome measure of current depression severity as this scale was designed to be sensitive to change.*
Secondary		
The secondary objective(s) are to determine the effect of iTBS on DLPFC rfMRI and establish a relationship between change in brain resting state functional connectivity and treatment effects.	*To assess the effect of active HDS-TBS on the functional connectome, we will test for differences in DLPFC-SGACC connectivity between the active- treated and sham-treated after 5 days of treatment.*	*We will examine the connectivity between DLPFC-SGACC, using the DLPFC stimulation site, identified on neuronavigation and an a priori defined SGACC ROI.*
Tertiary		
N/A	*N/A*	*N/A*

4 STUDY PLAN

4.1 Study Design

[Hypothesis 1: The null hypothesis is that there will be no difference in reductions in depressive symptoms by the end of the five-day treatment period. The alternative hypothesis is that, compared with sham, active TMS will result in a greater reduction in depressive symptoms by the end of the treatment period.

Hypothesis 2: The null hypothesis is that there will be no difference in the change in correlation from pre-treatment to post-treatment between the active and sham groups. The alternative hypothesis is that, compared with sham, active TMS will result in a greater increase in correlation of the dorsal lateral prefrontal cortex (DLPFC) with limbic regions, in particular with the subgenual cingulate cortex (SGACC). This is a superiority comparison, for active relative to sham.

Participants will be recruited and will receive the Structured interview for Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V), the Montgomery-Asberg Depression Rating Scale (MADRS), the Young Mania Rating Scale (YMRS), the Oldfield Assessment for Handedness (handedness will be included in data analysis but is not an exclusionary criterion), and screening for dementia (MMSE >24). Following informed consent, participants will receive double blind randomization to active treatment with intensive iTBS rTMS or sham treatment. Participants will have a structural MRI, diffusion tensor MRI (DTI) and functional connectivity rs-fMRI scan. Both active and sham treatment will consist of 5 days of HDS-TBS treatment. We will optimize TMS coil positioning on an individual basis as described in **individualized targeting of TMS to DLPFC target. On Day 2 or 3 of treatment, patients will have option to complete an additional MRI, contingent on availability and scheduling.** At the end of each 5-day treatment patients will again receive an fMRI scan (one at pre-treatment and 1 at post-treatment). Participants will also receive the Scale for Suicide Ideation (SSI), Hamilton Depression Rating Scale (HAM-D), additional validated self-report questionnaires, and neurocognitive assessment at pre and post-treatment. During each day of treatment, patients will complete MADRS, SSI, and YMRS to track progress. There are options for participants to complete visits remotely as possible (such as screening). The participant will also return for a 4 week follow up visit to complete MADRS, HAM-D, SSI, and YMRS. For the pre-treatment and post-treatment sessions, patients will be given the option to complete “The Battleship Task”; this is a computer-based cognitive task which examines how well patients are able to learn a set of shapes that are hidden on a grid. See “Schedule of Activities” in Section 12.1 for more detailed breakdown of the tasks per visit.

Patients will follow the recommended treatment course as best as possible. The protocol does allow for variability in the treatment timeline contingent on patient availability, MRI availability, and other scheduling factors. In this case, we are able to accommodate the participants who can not commit for 5 consecutive days or when one of these 5 days will fall on holiday. Thus, we will be able to complete the treatment course within 7-10 days.

Treatment Assessments
Primary outcome measure-Depression severity will be measured using the clinician administered Montgomery-Asberg Depression Rating Scale (MADRS). We have used the MADRS in many prior studies. The MADRS will be the primary outcome measure of current depression severity as this scale

was designed to be sensitive to change. It consists of 10 items, each of which has severity ranges with a total range of 0-60.

Treatment with High Dose Theta-burst Stimulation Procedures
Stimulation Parameters: Each participant's resting motor threshold will be determined using EMG recordings and the adaptive parameter estimation by sequential testing (PEST) algorithm, to ensure accuracy and reproducibility. Treatment sessions: iTBS will be delivered at the individually targeted DLPFC site at 90% RMT. The stimulation pattern and total number of pulses will be triplet 50 Hz bursts, repeated at intervals of 200 ms (5 Hz); 2 s on and 8 s off; 1800 pulses per session; total duration of 10 min [6]. There will be ten iTBS stimulation sessions/day on 5 sequential days. Stimulation will be double-blinded. Neuroimaging sessions will be conducted prior to iTBS treatment ('pre') and ideally 24 hours following day 5 of treatment ('post').

Sham iTBS**.** For both active and sham iTBS, we will use the Magventure Cool B65 A/P coil. The sham treatment works by blocking the magnetic field with an internal spacer on the sham side, allowing the operator to place the appropriate coil surface (active vs. sham) against the scalp. During the sham iTBS, we will use the coil's electric stimulation functionality that allows for the delivery of a brief electric pulse to the scalp simultaneous to the TMS pulse to mimic the scalp sensation during the sham condition. Importantly, the electric pulse is calibrated to the stimulator output to ensure a realistic sham condition. Blinding Procedures: will be implemented to control for expectancy effects related to TMS stimulation. Persons who will be blind to TMS status are patients and all study staff with the exception of Dr. Kevin Lynch (the study statistician) and Dr. Michael Thase (clinical and medical monitor). Included in blinded status is the TMS operator since "active" vs "sham" delivery will be randomized and delivered in a blinded fashion (see above).

Neuronavigation. Prior to the iTBS visits, target coordinates and orientation vectors will be generated from the fMRI data and the e-field models, and loaded into the Brainsight neuronavigation system along with the subject's reconstructed T1 image. Scalp and cortical surfaces will be generated from the T1. During the visits, the subject will be co-registered to the T1 using fiducial points at the Nasion, Tragi and nose tip. TMS pulses will be delivered to the target at the optimal orientation, and the accuracy of this targeted stimulation will be monitored and tracked by the Brainsight software.

Individualized electric-field modelling to optimize stimulation for the chosen target. Cortical anatomy varies across subjects and this variability can impact the magnitude of the electric field generated by the TMS pulse at the target. For instance, cortical gyrification creates transitions between gray matter and cerebrospinal fluid, influencing the local e-field distribution in an orientation dependent manner. In addition, conductivity anisotropy in large white matter fiber bundles leads to preferential directions for current flow, further impacting the e-field generated by TMS. To account for these sources of variability, we will use the structural and diffusion data to create finite-element models of the electric field for varying coil orientations at the individualized site of stimulation and use these models to optimize the coil orientation for each subject [7].

Neuroimaging procedures.
MRI data will be acquired on a 3 Tesla Siemens Prisma scanner using a 64 channel head coil (Erlangen, Germany). Our acquisitions are optimized for Siemens Prisma scanners and are rigorously tested as part of the human connectome project (HCP). In the rs-fMRI targeting session T1-weighted, T2-weighted, , and rs-fMRI (2x 8 min) scans will be collected using the 64-channel head coil.]

4.2 Scientific Rationale for Study Design

[The project is testing whether using high dose spaced theta-burst rTMS (HDS-TBS) produces a significant reduction in depressive symptoms and uses a comparison with sham.]

4.3 Justification for Dose

[N/A – This project does not include dosage of medication.]

4.4 End of Study Definition

[A participant is considered to have completed the study if they have completed all phases of the study shown in the Schedule of Activities (SoA), Appendix Section 12.1.]

5 STUDY POPULATION

5.1 Inclusion Criteria

[In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Bipolar depression (BP I and BP II) by DSM 5 criteria [8]
- Age 18-70
- Right or left handed
- All genders
- Treatment resistant depression, as in they must have treatment resistant depression with 2 or more prior antidepressant trials that have failed to produce a response (> 50% reduction in symptoms) using ATHF criteria [9]
- Able to provide informed consent to participate in the study
- Must be on a stable medication regimen, requiring at least one mood stabilizer
- Depression severity as represented by scoring at least 20 on MADRS

If unsure about participants' eligibility, the research team may contact the participants' treatment provider (i.e. psychologist, nurse practitioner, psychiatrist) to gather additional information to make a determination.]

5.2 Exclusion Criteria

[An individual who meets any of the following criteria will be excluded from participation in this study:

- No current substance abuse disorder for the past 6 months (previous substance abuse not exclusionary)
- Any psychotic disorder or current active psychotic symptoms (personality disorders not exclusionary unless in the opinion of the referring psychiatrist it would jeopardize participation)
- No dementia or other major neurological disorders
- Not having depression as primary disorder
- No major medical illness, for example metastatic cancer, end stage renal disease
- Not able to verify contact information. Participants must be able to follow through with the study & must have verified contact information and at least one verified contact
- Pregnancy. While there are no known risks to a fetus this is a new use of TMS, which has not been tested, thus pregnancy is exclusionary
- Score on YMRS greater than 12 (patients with mixed features have been shown not to respond well to TMS treatment [10])
- Rapid cycling Bipolar illness (patients with > 4 mood episodes within the past year will be excluded, as they have a higher risk of switch to mania [11])

- Any implants, conditions, or contraindications that would be deemed unsafe for TMS or MRI
- Currently using benzodiazepines (such as lorazepam) with a dose >1 mg per day or equivalent]

5.3 Lifestyle Considerations

[Patients will not be asked to discontinue their outside treatment. There is no evidence suggesting that compounding treatments may worsen depressive symptoms.]

5.4 Screen Failures

[Screen failures are defined as participants who consent to participate in the clinical trial but are found to be ineligible during or after screening. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information may include: demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of current depressive symptoms or treatments may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.]

5.5 Strategies for Recruitment and Retention

[All participants will be recruited through the University of Pennsylvania resources and the surrounding community.

Patients can express interest by initiating contact with the research staff for a center wide phone or self-report screening. Responses will be stored in REDCap and reviewed by study coordinators. Patients who meet inclusion and exclusion criteria will be invited to the screening visit.

All recruitment materials, including but not limited to self-report screening, phone screening, flyers, brochures, referral letters, online postings, and email templates will be IRB-approved before distribution.]

6 STUDY INTERVENTION

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

Name of Device	*Manufacturer*	*Marketing Status in the U.S.*	*FDA Device Classification (I, II, III)*
MagPro X100	*MagVenture*	*FDA approved*	*II*
Cool-B65 A/P	*MagVenture*	*FDA approved*	*II*

6.1.2 Dosing and Administration

[Prior to beginning treatment, participants will undergo resting motor threshold (RMT) to determine the level of ideal for the stimulation sessions. During treatment (day 1-5), iTBS will be delivered at the individually targeted DLPFC site at 90% RMT. The stimulation pattern and total number of pulses will be triplet 50 Hz bursts, repeated at intervals of 200 ms (5 Hz); 2 s on and 8 s off; 1800 pulses per session; total duration of 10 min [6]. There will be ten iTBS stimulation sessions/day on 5 sequential days.]

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and accountability

[All interventional devices are owned, stored, and managed by the Center for Neuromodulation in Depression and Stress (CNDS).]

6.2.2 Formulation, Appearance, Packaging, and Labeling

[Devices are already owned and set up by the CNDS. Trained staff will check and prepare the devices as needed throughout the study.]

6.2.3 Product Storage and Stability

[All devices are stored behind locked doors with access restricted to members of the CNDS. These devices are located in the CNDS lab-space in the Richards Biomedical Building. Devices are stored and set up as per manufacturer requirements/recommendations.]

6.2.4 Preparation

[Devices are already set up in the CNDS lab-space.

Prior to the iTBS visits, target coordinates and orientation vectors will be generated from the fMRI data and the e-field models, and loaded into the Brainsight neuronavigation system along

with the subject's reconstructed T1 image. Scalp and cortical surfaces will be generated from the T1. During the visits, the subject will be co-registered to the T1 using fiducial points at the Nasion, Tragi and nose tip. TMS pulses will be delivered to the target at the optimal orientation, and the accuracy of this targeted stimulation will be monitored and tracked by the Brainsight software.

Motor threshold will be determined prior to TMS administration. Throughout the course of the treatment, trained staff will check the machine before use and set the machine to the necessary parameters.]

6.3 Measures to Minimize Bias: Randomization and Blinding

[Patients who are enrolled in the study (i.e., met inclusion/exclusion criteria) will be randomized to active TMS or Sham by a randomization system determined by the Independent Randomization Provider (IRP). This will occur at least one day before the start of treatment.

Only trained staff will administer the TMS treatment and the required clinical assessments during the study visits. These staff (as well as the PI and the patients) will also be blinded until the end of the study. Included in blinded status is the TMS operator since "active" vs "sham" delivery will be randomized and delivered in a blinded fashion. The only exception will be Dr. Kevin Lynch (the study statistician) and Dr. Michael Thase (clinical and medical monitor).]

6.4 Study Intervention Compliance

[Trained staff will administer TMS and monitor patients throughout treatment. They will use an SOP to ensure study compliance, including tracking the necessary TMS sessions. Dr. Thase will act as clinical and medical monitor to ensure intervention compliance.]

6.5 Concomitant Therapy

[For this protocol, patients may have an existing treatment regimen outside of the trial (i.e., antidepressant medication or mood stabilizers). Prior to enrolling, patients will be asked about any outside treatments and must have been enrolled in their treatment for at least 4 weeks prior to completing the baseline for this trial. This will be confirmed during screening visits as well. Patients will be asked to continue their same treatments during study participation.]

6.5.1 Rescue Medicine

[N/A - This study will not supply rescue medication.]

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

[N/A – Patients are not able to remain in the trial without enrolling in the treatment. Discontinuation from the TMS will mean discontinuation from the study. Ending TMS due to AE will be documented and patient will be evaluated for safety.]

7.2 Participant Discontinuation/Withdrawal from the Study

[Participants are free to withdraw from participation in the study at any time upon request. The PI may discontinue or withdraw a participant from the study for the following reasons:

- Participants may be withdrawn from the study by staff if deemed necessary for their health or safety.

We anticipate that some participants may withdraw. We do not expect early termination of participation due to patient or investigator withdrawal to have any impact on safety or well-being of participants. Patients who withdraw for AE will be evaluated by trained staff for safety.

Participants who enroll in the study (i.e., sign consent and pass screening) and are subsequently withdrawn will be replaced.]

7.3 Lost To Follow-Up

[A participant will be considered lost to follow-up if they fail to return for a scheduled visit and/or are unable to be contacted by the study site staff. If a patient fails to appear for a scheduled visit, staff will attempt to contact and reschedule if the patient wishes and is able to continue in the study. Staff will reach out at least 3 times, and if patient continues to be unreachable, they will be considered lost to follow-up.]

8 STUDY ASSESSMENT AND PROCEDURES

8.1 Efficacy Assessments

[Participants complete the following for screening: Structured interview for Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V), the Montgomery-Asberg Depression Rating Scale (MADRS), the Young Mania Rating Scale (YMRS), the Oldfield Assessment for Handedness (handedness will be included in data analysis but is not an exclusionary criterion), and screening for dementia (MMSE >24).

Once enrolled, patients will also complete an MRI scan. MRI data will be acquired on a 3 Tesla Siemens Prisma scanner using a 64 channel head coil (Erlangen, Germany). Our acquisitions are optimized for Siemens Prisma scanners and are rigorously tested as part of the human connectome project (HCP). In the rs-fMRI targeting session T1-weighted, T2-weighted, , and rs-fMRI (2x 8 min) scans will be collected using the 64-channel head coil. We will use the structural and diffusion data to create finite-element models of the electric field for varying coil orientations at the individualized site of stimulation and use these models to optimize the coil orientation for each subject [12].

Patients will complete the TMS administration for 5 consecutive days. They will also complete the MADRS on each day. Following completion of treatment, participants will complete another MRI scan and another MADRS. Patients will also complete a Scale for Suicide Ideation (SSI) and neurocognitive assessments pre and post-treatment.

The data collected to be included in efficacy analyses (pre- and post-treatment) will be the measures of depression severity (MADRS), Antidepressant Treatment History Form (ATHF) data, psychotropic medication at baseline, an optional “The Battleship Task” computational task (which examines how well participants are able to learn a set of shapes that are hidden in a grid), and resting state functional connectivity data (using DLPFC as a seed regions). The primary outcomes will be response to TMS as evidenced by change in MADRS scores for depression severity from the pre-treatment baseline to the end of the 5-day treatment course. The secondary outcome will be change in functional connectivity from pre-treatment to post-treatment using MRI of the brain.]

8.2 Safety and Other Assessments

[Participants will complete the following in order to determine their eligibility for the project: Structured interview for Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V), the Montgomery-Asberg Depression Rating Scale (MADRS), the Young Mania Rating Scale (YMRS), the Oldfield Assessment for Handedness (handedness will be included in data analysis but is not an exclusionary criterion), and screening for dementia (MMSE >24).

In addition, patients will complete safety screening for both the MRI scan and the TMS administration, screening out individuals who may not be able to complete these tasks.

Throughout treatment, patients will be monitored by certified personnel. MADRS will be completed during each day of TMS treatment, which will allow staff to monitor symptom severity for safety as well. Any safety concerns will be brought to the PI and necessary personnel.]

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events (AE)

[An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. Intercurrent illnesses or injuries should be regarded as adverse events. A pre-existing condition should be recorded as an adverse event if the frequency, intensity or the character of the condition changes.]

8.3.2 Definition of Serious Adverse Events (SAE)

[Serious Adverse Events (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that, in the view of the sponsor-investigator, is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.
- required intervention to prevent permanent impairment or damage (for devices only)

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.]

8.3.3 Unanticipated Adverse Device Effect (UADE)

[Unanticipated Adverse Device Effect (UADE)

A UADE is any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously

identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.]

8.3.4 Classification of an Adverse Event

8.3.4.1 Severity of Event

[For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

8.3.4.2 Relationship to Study Intervention

[All adverse events (AEs) must have their relationship to the TMS administration assessed by the PI. The degree of certainty about causality will be graded using the categories below.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related – A clinical event whose temporal relationship TMS administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- Unrelated – The AE is completely independent of TMS administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

8.3.4.3 Expectedness

[The PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for TMS.]

8.3.5 Time Period and Frequency for Event Assessment and Follow-Up

[Safety will be assessed by monitoring and recording potential adverse effects at each study visit. Information on all adverse events will be recorded in the source documentation. To the extent possible, each adverse event or follow-up information will be evaluated by the PI. This allows site to determine relationship to treatment, expectedness, and seriousness of the event. It also allows the site to evaluate patient safety and work with the patient to a resolution.]

8.3.6 Adverse Event Reporting

[Adverse events will be reported from the time of informed consent until study completion. The investigator will report AEs to the IRB and other local regulatory groups per the local requirements.]

8.3.7 Serious Adverse Event Reporting

[The PI will report unexpected and related adverse events to the necessary regulatory groups.]

8.3.8 Reporting Events to Participants

[Adverse events (both individual and aggregate level) will be shared with participants as the PI finds necessary.]

8.3.9 Events of Special Interest

[As per MRI procedure dictates, it is possible that during the course of the research study, the research staff may notice unexpected finding(s) on a participant's images. Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform participants if necessary for medical follow-up. These possible finding(s) will not be disclosed to the participant unless deemed necessary by the PI and reviewing radiologist in order to avoid unnecessary anxiety for participants.

Other notable events, such as device malfunctions, will be documented and reported as needed.]

8.3.10 Reporting of Pregnancy

[N/A - All women of child bearing potential are asked if they are using a reliable method of birth control and are asked to attest that they are not pregnant before study visit and on the TMS safety screening form. Due to potential safety reasons, pregnant women will not be included in the study.]

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UP)

[The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.]

8.4.2 Unanticipated Problem Reporting

[Unanticipated problems (UPs) should be reported by the PI to the necessary regulatory groups, within the timeline required by local regulations.]

8.4.3 Reporting Unanticipated Problems To Participants

[Unanticipated problems (both individual and aggregate level) will be shared with participants as the PI finds necessary.]

8.5 Device Reporting

[Safety reporting for the device(s) will be according to 21 CFR 812.150.]

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

- Primary Efficacy Endpoint(s):

[The primary outcome will be based on the set of repeated Montgomery Asberg Depression scores obtained at baseline and on each of the five treatment days.

Hypothesis 1: The null hypothesis is that there will be no difference in reductions in depressive symptoms by the end of the five-day treatment period. The alternative hypothesis is that, compared with sham, active TMS will result in a greater reduction in depressive symptoms by the end of the treatment period. This is a superiority comparison, for active relative to sham.]

- Secondary Efficacy Endpoint(s):

[The main secondary outcome will be the change in correlation of the dorsal lateral prefrontal cortex (DLPFC) with limbic regions, in particular with the subgenual cingulate cortex (SGACC).

Hypothesis 2: The null hypothesis is that there will be no difference in the change in correlation from pre-treatment to post-treatment between the active and sham groups. The alternative hypothesis is that, compared with sham, active TMS will result in a greater increase in correlation of the dorsal lateral prefrontal cortex (DLPFC) with limbic regions, in particular with the subgenual cingulate cortex (SGACC). This is a superiority comparison, for active relative to sham.]

9.2 Sample Size Determination

[The sample size provides power for a large effect on the primary hypothesis, comparing the treatment groups on improvements in their MADRS scores across five days of treatment. Analyses will be based on linear mixed effects models, as described below.

Power for Hypothesis 1: We use the methods of Hedeker, Gibbons and Waternaux [13]. For a random intercept model with correlation coefficient of rho=0.3, we have 80% power for a group effect of Cohen's d=0.72.

Further analyses are regarded as exploratory. The sample will provide preliminary effect size estimates for secondary endpoints, for future studies.]

9.3 Populations for Analyses

[The analyses will follow the Intention-to-Treat principle, with all randomized participants contributing to analyses. In particular, the linear mixed effects models to be used for the primary hypothesis will make use of all data, partial or complete, provided by the participants.]

9.4 Statistical Analyses

9.4.1 General Approach

[The analyses of the outcomes of Aims 1 and 2 will use linear mixed effects models for repeated measures. Outcomes will be measured at baseline and for each of the 5 days of TMS treatment. The model will incorporate baseline covariates (age, gender, ATHF score, use of psychotropic medication, handedness, head motion), along with randomized treatment assignment. The data collected to be

included in efficacy analyses (pre- and post-treatment) will be the measures of depression severity (MADRS), Antidepressant Treatment History Form (ATHF) data, psychotropic medication at baseline and resting state functional connectivity data (using DLPFC as a seed regions). If other variables are found to be related to the outcome and are imbalanced with respect to treatment assignment, we will perform additional analyses with these variables added to the model. For the continuous outcomes, data transformations will be implemented if there are substantial deviations from normality.

Effect size estimates and associated confidence intervals will be reported for all primary and secondary outcomes.

The trajectory of changes over the 5 days of treatment will be assessed with descriptive statistics and graphical displays. We will plot the mean daily changes in each score by treatment group to provide insight into the typical trajectory of treatment response. Because this is a short-term study we do not anticipate much (if any) missing data.]

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

[Aim 1: To assess clinical efficacy of HDS-TBS.

Hypothesis 1: Compared with sham, active TMS will result in a greater reduction in depressive symptoms by the end of the treatment period. Each patient will receive either one five day sham or one 5-day active treatment.

The primary outcome will be based on the set of repeated Montgomery Asberg Depression scores obtained at baseline and on each of the five treatment days. We will use linear mixed effects models to compare the two treatment groups on change from baseline across the five days. As noted above, the response may be transformed to reduce levels of skewness. The main fixed effects will be the treatment group indicator, and we expect that a random intercept will accommodate the within person correlations over the five daily measures of change.

Power for Hypothesis 1: We use the methods of Hedeker, Gibbons and Waternaux [13]. For a random intercept model with correlation coefficient of rho=0.3, we have 80% power for a group effect of Cohen's d=0.72.

Estimated regression coefficients will be reported, along with standard errors, associated confidence intervals, and p-values for hypothesis tests. In analyses adjusting for covariates, adjusted least squares means for treatment groups will be reported.

Little missing data is expected for the baseline and five-day treatment period. The mixed effects models used for Hypothesis 1 will use any data, partial or complete, provided by the randomized participants, and will yield valid estimates under missing-at-random assumptions.]

9.4.3 Analysis of the Secondary Endpoint(s)

[Aim 2: To determine the effect of iTBS on DLPFC rsfMRI establish a relationship between change in brain resting state functional connectivity and treatment effects

Hypothesis 2: Compared with sham, active TMS will result in a greater increase in correlation of the dorsal lateral prefrontal cortex (DLPFC) with limbic regions, in particular with the subgenual cingulate cortex (SGACC).

To assess the effect of active HDS-TBS on the functional connectome, we will test for differences in DLPFC-SGACC connectivity between the active- treated and sham-treated after 5 days of treatment. We will implement a linear regression model with change in connectivity score as the dependent variable, and age, gender, ATHF score, and use of psychotropic medication as covariates. We will examine the connectivity between DLPFC-SGACC, using the DLPFC stimulation site, identified on neuronavigation and an a priori defined SGACC ROI. We will follow Dosenbach et al.'s approach [14]for seed-based analyses to test resting state connectivity between these a priori ROIs. Functional connectivity analyses will be conducted by placing a seed (sphere with 5mm radius) in the DLPFC ROI. DLPFC seeds will match coordinates used for individual TMS coil placement. ROIs will be individually anatomically based and identified using anatomical masks on each participant's T1 volume aligned to each participant's rs-fMRI data using Boundary Based Registration [15]. Average BOLD time-series data will be extracted from each ROI, for each participant, and used to calculate correlation coefficients for values at baseline and end of each 5-day treatment. These will be converted to individual z-scores using Fisher's transformation, yielding the indices representing RSFC between the seed and targets. We will use a linear mixed effects model to compare the pre- to post-treatment between-group change across the sham and active conditions. We expect that as in a previous study using HDS-iTBS, the anticorrelation between SGACC and DLPFC will increase following treatment.

Estimated regression coefficients will be reported, along with standard errors, associated confidence intervals, and p-values for hypothesis tests. In analyses adjusting for covariates, adjusted least squares means for treatment groups will be reported.

Little missing data is expected for the baseline and five-day treatment period. The mixed effects models used for Hypothesis 2 will use any data, partial or complete, provided by the randomized participants, and will yield valid estimates under missing-at-random assumptions.]

9.4.4 Safety Analyses

[N/A]

9.4.5 Baseline Descriptive Statistics

[We will calculate descriptive statistics to allow adequate characterization of the sample. We will not use inferential statistics to compare the baseline groups.]

9.4.6 Planned Interim Analyses

[N/A]

9.4.7 Sub-Group Analyses

[N/A]

9.4.8 Tabulation of Individual Participant Data

[Individual participant data will be listed for pre and post measurements.]

9.4.9 Exploratory Analyses

[We hypothesize that following treatment those who received active HDS-TBS will have an increase in the anticorrelation of DLPFC-sgACC connectivity compared with pre-treatment and that the change in connectivity will be correlated with the change in depression severity. Analyses may be conducted on this. Additional analyses may be updated as needed in the future.]

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent and Other Informational Documents Provided To Participants

[Consent forms describing in detail the TMS administration, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to enrolling in the study. Participants completing screening remotely will sign electronically in an IRB compliant system, such as REDCap. Consent materials are submitted with this protocol.]

10.1.1.2 Consent Procedures and Documentation

[Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The site will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants can have the opportunity to discuss the study with their family or doctors or think about it prior to agreeing to participate if needed. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Participants completing screening remotely will sign electronically in an IRB compliant system, such as REDCap.]

10.1.2 Study Discontinuation and Closure

[This study may be temporarily suspended or prematurely terminated by the Funding Sponsor or the PI at any site if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and funding sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding sponsor, IRB and/or Food and Drug Administration (FDA).]

In terminating the study, the Sponsor-Investigator will assure that adequate consideration is given to the protection of the subjects' interests.]

10.1.3 Confidentiality and Privacy

[Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without necessary prior written approval.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the funding sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or other requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored to IRB compliant online databases, such as REDCap. PHI will be stored separately in secure cabinets inside locked rooms. Coded data will be stored on a secure server at the University of Pennsylvania through the Neuroscience Neuroimaging Group computing cluster. MRI data are securely copied on the uphs network directly from the MRI machine at Stellar Chance to this computing cluster without separate physical storage. Coded data are directly uploaded to the computing cluster from the computers on which the data are collected. The Penn computers are in a secured lab space and connected directly to the uphs encrypted network. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected.]

10.1.4 Future Use of Stored Specimens and Data

[Data collected for this study will be analyzed and stored to IRB compliant online databases, such as REDCap. De-identified data may be shared with approval from necessary committees with other investigators, with formal data-sharing agreement.]

10.1.5 Safety Oversight

[This is a low-risk study. Subject safety will be closely monitored. Subjects reporting side effects will be used to evaluate individual safety of iTBS. The PI will be monitoring the ongoing safety of subjects. PI is responsible for monitoring the data quality and the ongoing safety of subjects at respective site.]

10.1.6 Clinical Monitoring

[Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). Dr. Thase will work with the PI to ensure clinical monitoring is completed.]

10.1.7 Quality Assurance and Quality Control

[The site will perform internal quality management of study conduct, data collection, documentation and completion. All monitoring and audits are to be performed according to ICH GCP E6(R2). The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor-investigator, and inspection by local and regulatory authorities.]

10.1.8 Data Handling and Record Keeping

10.1.8.1 Data Collection and Management Responsibilities

[Data collection is the responsibility of site under the supervision of the PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data and follow ALCOAC standards (attributable, legible, contemporaneous, original, accurate, and complete).

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.]

10.1.8.2 Study Records Retention

[Study documents will be retained for the necessary time, as required by local regulations.]

10.1.9 Protocol Deviations

[The PI and the study team should document all scenarios where the protocol is not followed. They should assess whether the deviation is considered of significant impact (such as increasing risks to participants, etc.) and should be reported as required, with suggestions for corrective plans to prevent such occurrences.]

10.1.10 Publication and Data Sharing Policy

[This study will comply with the data sharing agreement. De-identified data may be shared with approval from the necessary committees with other investigators, with formal data-sharing agreements.]

10.1.11 Conflict of Interest Policy

[The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.]

10.2 Additional Considerations

[N/A]

10.3 Protocol Amendment History

Version	*Date*	*Description of Change*	*Brief Rationale*
V1.1	1/28/2022	Changes for resubmission	Changes for resubmission
V1.2	3/24/2022	Amendments in protocol of scan and task procedures, remote options	Better capture progress in trial, allowing for more flexibility
V1.3	8/03/2022	Amendments in protocol of task procedures and treatment timeline	Incorporate additional measure for cognitive changes and include more flexibility for treatment course; optional task was also included

Version	*Date*	*Description of Change*	*Brief Rationale*

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12 APPENDIX

12.1 Schedule of Activities (SoA)

Procedures	Screening	*Enrollment/* Baseline	TMS Session Day 1	TMS Session Day 2	TMS Session Day 3	TMS Session Day 4	TMS Session Day 5	Post Stimulation	*Follow-Up* Visit (4 weeks)
Informed consent	X								
Demographics	X								
Medical history	X								
SCID	X								
MADRS	X		X	X	X	X	X	X	X
HAM-D	X							X	X
SSI	X		X	X	X	X	X	X	X
YMRS	X		X	X	X	X	X	X	X
Oldfield Assessment for Handedness	X								
MMSE	X								
The Battleship Task		X						X	
Randomization		X							
MRI		X		X*	X*			X	
Motor Threshold		X							
Neurocognitive assessments		X						X	
TMS treatment (1 session every 50 minutes, 10			X	X	X	X	X		

sessions per day)									
Self Report Questionnaires	X		X	X	X	X	X	X	X

*MRI: Optional MRI scan on Day 2 or 3 of TMS treatment.

**Battleship Task: Optional task given at baseline and post treatment

END OF DOCUMENT