ACCELERATED TMS TO A NOVEL BRAIN TARGET IN MDD AND PTSD

A clinical trial to study of the effects of fMRI-guided rTMS treatment for Major Depressive Disorder and Post-Traumatic Stress Disorder

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Investigational Product: MagPro X100* magnetic stimulator
Cool-B65 Butterfly Coil

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Table of Contents

Contents

List of Abbreviations

CAMRIS: Center for Advanced Magnetic Resonance Imaging and Spectroscopy

CNDS: Center for Neuromodulation in Depression and Stress

DBS: Deep Brain Stimulation

DLPFC: Dorsolateral Prefrontal Cortex

fMRI: Functional Magnetic Resonance Imaging

LPFC: Lateral Prefrontal Cortex

rTMS: Repetitive Transcranial Magnetic Stimulation

SAE: Significant Adverse Event

sgACC: Subgenual Anterior Cingulate Cortex

TBS: Theta-Burst Stimulation

TMS: Transcranial Magnetic Stimulation

Study Summary

Title	Accelerated TMS protocol for modulating neural circuitry relevant to affective illness
Short Title	Mini-TBS Trial
IRB Number	TBD
Protocol Number	N/A
Phase	I
Methodology	cross-sectional treatment
Study Duration	8 months (Screening, 9 weeks of treatment visits with a 3-week break, and 6 months of phone/survey follow-up visits)
Study Center(s)	Center for Neuromodulation in Depression and Stress University of Pennsylvania School of Medicine Department of Psychiatry
Objectives	We aim to compare the efficacy of rTMS treatment to two sub-regions of the Dorsolateral Prefrontal Cortex (DLPFC). We will examine the standard positioning of TMS used in clinical settings compared with TMS using MRI to guide the precise location of stimulation. We hypothesize that fMRI-guided TMS will produce greater benefit to patients with MDD/PTSD than the standard targeting method for TMS.
Number of Subjects	N=80; n=40
Main Inclusion and Exclusion Criteria	18-60; inclusive; no TMS contraindications; no medication use that substantially reduces seizure threshold or interferes with fMRI recordings; PTSD diagnosis or trauma induced MDD (SCID interview) and elevated depression (PHQ ≥ 10).
Investigational Product (drug, biologic, device, etc.)	MagVenture devices for rTMS administration include: -MagPro X100* magnetic stimulator -Cool-B65 Butterfly Coil
Duration of administration (if applicable)	2 sets of 10 consecutive weekdays (at minimum 4 sessions per week with a total of 10 overall sessions per set)
Reference therapy	N/A
Statistical Methodology	Clinical outcome will be evaluated on symptom scales in a TMS target x Time ANOVA. Similarly, rate of change (slope) x TMS Target will indicate how rapidly each treatment improves symptoms.

Safety Evaluations	TMS protocols will be administered by specially-trained staff from the Center for Neuromodulation in Depression and Stress the University of Pennsylvania Department of Psychiatry. All TMS staff will be trained by the PI (Desmond Oathes, Ph.D.) and the Center Director (Yvette Sheline, M.D.).
Data and Safety Monitoring Plan	The PI will be responsible for monitoring the data quality and the ongoing safety of subjects.

BACKGROUND AND STUDY RATIONALE

Introduction

This study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including [as applicable include the following regulations as they apply 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, and 812 and Good Clinical Practice: Consolidated Guidelines approved by the International Conference on Harmonisation (ICH). *Note: Only include ICH compliance if the study will actually comply with these requirements.] All episodes of noncompliance will be documented.*

1.1 Background and Relevant Literature

The subgenual Anterior Cingulate Cortex (sgACC) has been well established as a brain area sensitive to negative mood inductions and implicated in neural abnormalities associated with affective and stress disorders. It is therefore one of the primary targets for deep brain stimulation (DBS) treatment of MDD using surgically implanted DBS devices. Recent posthoc imaging studies of patients who have undergone TMS treatment for depression suggest that treatment outcomes tended to be better when patients were by chance stimulated in an area of lateral prefrontal cortex that had high levels of functional connectivity with sgACC. Based on this finding and on our own interleaved TMS/fMRI probe data, we contend that targeting delivery of TMS to the brain surface non-invasively as indicated by sgACC resting functional connectivity may be especially effective in downregulating sgACC and thereby producing superior clinical outcomes. We have used TMS/fMRI to better understand causal communication among circuits typically examined with resting fMRI alone (Chen et al., 2013). Our recent work suggests that there are specific sites that, when stimulated, influence subcortical brain areas implicated in affective disorders such as the sgACC. Previously, we targeted TMS based on brain atlases mapped onto individual brain surfaces. This proposal will utilize more individualized targeting from participants own resting connectivity data to guide stimulation that we show is especially effective in influencing downstream brain areas of interest. We will focus on a target region that our data suggest is particularly effective at influencing the sgACC. As an alternative brain target, we will also test the efficacy of the dorsolateral prefrontal cortex as a target given its precedence as an FDA-approved stimulation site for remediating depressive symptoms. To increase generalizability to other disorders and to patients with comorbid anxiety and depression (the typical clinical profile), we will recruit patients who are diagnosed with PTSD or trauma induced MDD and who have elevated depression (PHQ). We will recruit them, scan them in the MRI to get anatomical and resting fMRI data to guide TMS, then will invite them to participate in two rounds of two-week TMS treatment to each site (order counterbalanced) with approximately one month between treatments. We will monitor depressive (MADRS), PTSD (PCL Checklist), and quality of life (WHOQOL) measures before, acutely after, and every month for 6 months following TMS treatments to evaluate the effectiveness of each site in mitigating symptoms or improving functioning. A typical, FDA-approved clinical application of TMS involves long trains of repetitive TMS applied for approximately 40 minutes, 5 days/week, over 2-6 weeks, for a total of 10-30 TMS visits. The present study utilizes the same FDA-approved devices (Magventure Cool-Coil B65, MagVenture X100 Stimulator) to administer treatment. We will be modifying the FDA-approved protocol to stimulate similarly to a well-replicated protocol, theta-burst stimulation (Huang et al., 2005). We have attached several additional examples of prior studies which have safely utilized TMS outside of its FDA-approved protocol, even in heightened doses. For instance, in prior studies subjects have received FDA-approved 3000 rTMS pulses, but done bilaterally instead of unilaterally (6000 total stimulations) every weekday over 4-6 weeks (see Bakker et al., 2015). Similarly, subjects have received 3600 rTMS pulses every weekday over 10 days (see Chistyakov et al., 2015), or 3000 rTMS pulses every weekday over 6 weeks (see O'Reardon et al., 2007). Another study applied the FDA-approved protocol in more than a double-dose, with 6800 stimulations to 1 site every weekday over 7 weeks average participation (Hadley et al., 2013). The present study utilizes fewer stimulations than the FDA-approved protocol, with each visit including a maximum of 3700 pulses. For additional information, please see Anderson et al., 2006 for demonstrations of the safety of repeated exposure to TMS. Likewise, please see Wagner et al., 2007 and Parkin et al., 2015 for reviews of the importance of TMS research and how our proposed studies fit in the present and growing body of literature.

1.2 Name and Description of the Investigational Product

This study will use investigational MagVenture devices for single-pulse and rTMS administration, including:

- MagPro X100* magnetic stimulator
- Cool-B65 Butterfly Coil

The MagPro X100* magnetic stimulator and Cool-B65 Butterfly Coil are FDA-approved for rTMS treatments of depression.

1.2.1 Clinical Data to Date

1.2.1.1 Clinical Studies in Adults

Repetitive TMS (rTMS) to the dorsolateral prefrontal cortex (DLPFC) is an FDA-approved treatment for major depressive disorder. A normal, FDA-approved clinical application of TMS involves long trains of repetitive TMS applied for approximately 40 minutes, 5 days/week, over 4-6 weeks, for a total of 20-30 TMS visits. Recent post-hoc imaging studies of patients who have undergone TMS treatment for depression suggest that treatment outcomes tended to be better when patients were by chance stimulated in an area of lateral prefrontal cortex that had high levels of functional connectivity with sgACC. Researchers have used TMS/fMRI to better understand causal communication among circuits typically examined with resting fMRI alone (Chen et al., 2013), suggesting there are specific sites that, when stimulated, influence subcortical brain areas implicated in affective disorders such as the sgACC.

This study will utilize individualized targeting from participants' own fMRI scans. We will focus on a target region that our preliminary data suggest is particularly effective at influencing the sgACC. As an alternative brain target, we will also test the efficacy of the standard dorsolateral prefrontal cortex (DLPFC) target.

1.3 Dose Rationale

Several prior studies have safely utilized TMS outside of its FDA-approved protocol, even in substantially larger doses. For instance, in prior studies subjects have received the FDA-approved 3000 rTMS pulses, but done bilaterally instead of unilaterally (6000 total stimulations) every weekday over 4-6 weeks (see Bakker et al., 2015). Similarly, subjects have received 3600 rTMS pulses every weekday over 10 days (see Chistyakov et al., 2015), or 3000 rTMS pulses every weekday over 6 weeks (see O'Reardon et al., 2007). Another study applied the FDA-approved protocol in more than a double-dose, with 6800 stimulations to 1 site every weekday over 7 weeks average participation (Hadley et al., 2013). The present study utilizes many fewer stimulations than these recent/established protocols, with each visit including a maximum of 3700 pulses (including motor threshold determination).

2 Study Objectives

We aim to establish the clinical efficacy of TMS stimulation using targets defined by resting connectivity in patients. We hypothesize that MRI-defined TMS will yield greater reductions in symptoms and greater improvements in quality of life among patients. In addition, we hypothesize that greater resting state connectivity will predict greater reductions in symptoms following TMS.

2.1 Primary Objective

- To assess and compare the clinical efficacy of rTMS treatments performed at the standard brain target versus an fMRI-guided brain target

2.2 Secondary Objectives (if applicable)

- To assess the correlation between resting-state connectivity prior to TMS and the degree of clinical change in response to TMS treatment targeting this circuit.

3 Investigational Plan

Visit #0: Consenting / Screening procedures
Visit #1/Baseline: Baseline MRI Scan to determine TMS targets, clinical assessments, and neuropsychological assessments
Visit #2-11: Targeting + TBS treatment and clinical assessments
Break: Subjects spend 3 weeks away from the lab,
(Phone/Survey) Visits #12 and 13: Clinical assessments
Visit #14-23: Targeting + TBS treatment and clinical assessments
(Phone/Survey) Visit #24-29: Clinical assessments
See Section 6. Study Procedures for specific assessments at each visit

3.1 General Design

TMS will be administered to either the fMRI-guided target or DLPFC in a randomized, single-blind design. 40 patients diagnosed with Post-Traumatic Stress Disorder (PTSD) or trauma induced Major Depressive Disorder (MDD) and symptoms of depression, as determined by meeting the DSM criteria for PTSD or MDD as a primary diagnosis and scoring ≥10 on the PHQ-9, will be recruited for this study. They will be otherwise healthy adults, aged 18-60, with PTSD or trauma induced MDD as primary diagnosis and without current diagnoses of significant, problematic substance use disorders or with present or past diagnoses of psychosis or bipolar illness. All subjects will receive active TMS, so there is no placebo or sham condition. However, the patients will be blinded as to whether their site of stimulation is based on the clinical standardized targeting method or our novel fMRI-guided targeting method. TMS is administered to one of these two sites over a two-week period, and then TMS will be administered to the other site over a subsequent two-week period following a three week wash out period. All subjects will receive TMS to both sites as a part of the study, but the order is randomized and counterbalanced. All participants will be recruited through the community via study advertisements and through the University of Pennsylvania and the VA. Subjects can express interest by contacting the study staff; in most cases, this will serve as the primary method for acquiring contact information. Physician referrals and the use of the Penn Data Analytics Center will also be incorporated as recruitment methods. Section 4.3 further elucidates all recruitment methods. Prior to any study visits, all subjects will be screened in a telephone interview with a trained member of the study staff or via a self-report screening survey. The first study session will consist of a consenting and extended screening visit. The information collected in this initial visit will determine if the subject meets all inclusion criteria. We will also demonstrate TMS to ensure the subject is comfortable with all study procedures. At the second study session, participants will undergo an MRI procedure for 60 minutes. This will be used to generate the TMS targets for the study. Subjects will then return every weekday (5 days per week, minimum of 4 days per week) over two weeks to receive the TMS treatment (10 sessions). These visits will last approximately 60 minutes each. The daily administration of TMS is a necessary component of the study, as it is consistent with the standard operating procedure for FDA-approved clinical TMS. During the 2 weeks of TMS treatment, subjects will undergo the many of the same clinical assessments used during the screening and baseline visits, in order to examine changes in symptoms. Subjects will then spend 3 weeks away from the study team; during the break, there will be two phone/survey visits used as a safety assessment. After this break, subjects will then return every weekday (5 days per week, minimum of 4 days per week) over two weeks to receive the TMS treatment (10 sessions) to the other site examined in the study. Upon completion of the study, scheduled phone and survey visits will take place every 4 weeks (+/- 7 days) over the subsequent 6-month period to monitor continued stability of clinical improvement and/or remaining clinical symptoms. Overall, this study consists of 1 consent/screening visit, 1 MRI scan, 20 total visits for TMS treatment, and 8 phone visits.

3.1.1 Screening Phase

Potential participants will be recruited from the community or they may be approached by collaborating clinicians (see recruitment plans) to explore participant's interest in taking part in a research study. Those who are interested will either complete a phone screen or self-report screening form via RedCap. Those who pass the screen will receive an appointment to come to the research location to review the informed consent form and conduct the baseline diagnostic assessment screen to determine eligibility. Informed consent will be obtained upon arrival at this initial visit and before any study-related procedures are conducted. All subjects will have the opportunity to ask questions before signing a consent form. The rest

of this initial visit will be an extended screening, which includes a structured diagnostic interview, psychiatric and medical evaluation, and collection of demographic information. Subjects will undergo a short demonstration of TMS to ensure that they are comfortable with all study procedures. This process involves adjusting the TMS device to a moderate level of stimulation and administering single pulses to the prospective TMS sites. A structured interview, *Diagnostic and Statistical Manual of Mental Disorders - DSM-5* will be used to assess the DSM criteria for PTSD or trauma induced MDD and the PHQ-9 will be used to assess presence of depressive symptoms. During the COVID-19 pandemic, the screening visit will be conducted virtually to limit in-person visits. The consent process will take place with a coordinator virtually and then documented via Recap (as discussed with the IRB in 2020). TMS would be tested at the second visit instead of at the screening visit.

3.1.2 Study Intervention Phase

Allocation to Interventional Group - Subjects will be randomly assigned to receive TMS at either the fMRI-guided target or the DLPFC during this study. This is a single-blind study, so the researchers will know the site of administration for each subject, whereas subjects will remain blinded. The research team will be responsible for randomizing subjects using a computer-based randomization algorithm.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The primary endpoint will be clinical improvement due to TMS at either of the two target regions. The study will focus on a target region of the fMRI-guided target and the standard DLPFC target, which is an FDA-approved rTMS treatment site. TMS-induced changes in brain activity are likely different for these two stimulation sites, despite their proximity. The aim of this study is to establish if using targets defined by resting connectivity in patients can be more effective at treating MDD/PTSD compared with standard targets.

3.2.2 Secondary Study Endpoints

The secondary endpoint to be analyzed in this study will be the relationship between baseline fMRI activity and the clinical improvement over the course of the study in the MDD/PTSD patients.

3.2.3 Primary Safety Endpoints

Study follow-up will be conducted monthly, over a 6-month period upon completion of the study in order to determine the duration and stability of clinical improvements. In addition, a clinical assessment will be conducted at the end of each 2-week administration of TMS to any changes in mood and/or symptoms across the study as it is completed.

4 Study Population and Duration of Participation

We plan to enroll 80 patients to obtain useable data from 40 patients diagnosed with PTSD or trauma induced MDD and symptoms of depression, as determined by meeting the DSM criteria for PTSD or trauma induced MDD and having a PHQ-9 score ≥ 10, will be recruited for this study. Participants will be otherwise healthy, aged 18-60, without significant concomitant diagnoses.

4.1 Inclusion Criteria

1. 18-60, male or female, any race
2. DSM-5 Diagnosis of PTSD or trauma induced MDD
3. PHQ-9 Score ≥10
4. Capacity to give informed consent and follow study procedures
5. English speaking

4.2 Exclusion Criteria

1. Significant handicaps (e.g. intellectual disability) that would interfere with testing procedures
2. MRI contraindications (e.g. foreign metallic implants, pacemaker, shrapnel or other metal in/on the body that cannot be removed, claustrophobia, etc.)
3. Additional TMS counter-indications (seizure disorder, CNS active disorder, certain medications described below)
4. Medication use that substantially reduces seizure threshold to TMS (olanzapine, chlorpromazine, lithium) and unwilling or unable medically to safely withdraw, at least two weeks prior to TMS, from these medications
5. Previous unsuccessful treatment with full trial of TMS, ECT, or deep brain stimulation (DBS).
6. Opiate medication
7. Known neurological disorders including multiple sclerosis, encephalopathy, seizure disorder, brain tumors
8. Current problematic alcohol or substance abuse disorder, bipolar disorder (as PI discretion), schizophrenia or other psychotic disorder.
9. Refusal to agree to abstain from illicit drug use for duration of the study
10. Refusal to agree to abstain from alcohol within 24 hours of scans
11. Pregnancy
12. Any other factor that in the investigators judgment may affect patient safety or compliance (e.g. distance greater than 100 miles from procedure site)
13. Currently taking psychiatric medications
14. Newly initiated psychotherapy (less than 6 weeks)

For patients wishing to discontinue medication: they must agree to work closely with their prescribing physician to wash off medications and the prescribing physician will be their point of contact if side effects or worsening of symptoms occurs.

4.3 Subject Recruitment

All participants will be recruited through the University of Pennsylvania, the Veterans Administration Medical Center, and surrounding community to find 80 patients with PTSD and trauma induced MDD and depressive symptoms. All subjects will express interest by initiating contact with the research staff or by confirming with their referring physician that they wish to be contacted for a screening procedure. All subjects fitting inclusion criteria will be approached by study staff to continue in the study. Additional recruitment methods will include Penn media services, social media, online advertisements (e.g. Craigslist), and fliers to be posted in the local community.

This study will also utilize Facebook as a recruitment resource. The CNDS Lab account will list posts on its page twice a week advertising for this specific study. This account is managed by Janet Stock.

In order to facilitate the enrollment of interested subjects in multiple studies, center-wide general pre-screening forms phone screen and self-report screen will be used. Because the Center for Neuromodulation in Depression and Stress has numerous studies that are all closely related, in both purpose and eligibility criteria, a general pre-screening (both phone and self-report) has been created. Many participants will be eligible for multiple studies and will be presented the opportunity to participate in all studies that they are eligible for. An additional benefit of a shared or general pre-screening is that participants who do not qualify for a specific study can be informed of other studies they are eligible for. It will be clearly explained to all individuals that this pre-screening is for multiple studies and that their information will be stored in REDCap.

Since approval of v1.0, the center-wide prescreening has successfully increased enrollment of eligible participants across studies as well as significantly reduced burden on interested participants and study staff. The proposed modification (Sept. 2019) to the screening form (v3.4) will update eligibility criteria to be more reflective of current protocols and reduce participant response burden by optimizing branching logic, clarifying language, and implementing standard symptom severity scales. This modification (v3.4) will not be available to potential participants until all actively enrolling CNDS studies obtain IRB approval. Until

that time, potential participants will continue to complete the currently approved version of the general screening form (v1.0).

We will also utilize the Penn Data Store as a recruitment aid. We will ask for a report from the PDS for individuals meeting our basic eligibility criteria, including a diagnosis of post-traumatic stress or adjustment disorder. We will request that the reports contain the following information: patient name, MRN, email, and phone; diagnosing provider & clinic name and date diagnosis was added to problem list. We will not ask for the diagnosis to be listed on this form or for any other PHI. We are only requesting information from outpatient, NON-mental health clinics. As this is a sensitive population, we will be contacting the diagnosing providers for permission to contact their participants who meet our basic criteria. This strategy has been discussed with Lauren Steinfeld (Privacy Office), David Heagerty (IRB) and Tracy Ziolek (IRB).

After receiving the list from PDS, we will then message the diagnosing providers via EPIC up to 2 times and attach the patient's record each time. EPIC messaging is a secure way to transmit PHI and all providers we wish to contact will have regular access to EPIC. In order to further protect patient privacy, we will not enter the patient's EMR. The patient's information that is visible when attaching a patient's record to an EPIC message is: Full Name, Age, DOB, Weight, Contact Information, PCP Name, MRN, Penn Medicine Status, and Next Appointment Date.

We will require that providers give expressed approval to contact each patient by indicating either Yes or No next to the patient's name. We will not accept a blanket approval for all of the provider's patients; however, we will accept a blanket request to not contact any of the provider's patients. If providers give us permission to contact their patients, we will contact the patient via email, if provided, with the Patient_Email. If no email is provided, we will call the patients up to 2 times and use the "Penn Data Store – Cure Accelerator Intro" script in the Phone Screen.

Student groups on campus: We may contact the chairs/leaders of student groups on campus who potentially have members that may be able to benefit from this study. We will not request any member information or attempt to contact any members directly; we will email the "StudentGroupEmail" (attached) to the chair of the group from the CNDS email account.

University Student Health and Mental Health Services: We may contact the clinical services on local university campus (including but not limited to Penn). We will send the"StudentServices" email, addressed to the providers at the clinics, requesting them to share the "StudentReferralLetter" with patients who they believe may benefit from this study and additionally requesting that they allow us to leave brochures or flyers within their clinics.

We will also list this study on our laboratory website at https://www.med.upenn.edu/cnds/

4.4 Duration of Study Participation

This study is expected to take place over 22 in-person study visits and 8 phone visits. The approximate amount of time that each study visit will take is outlined in Section 6. In-person visits will all take place over approximately 6-8 weeks. In addition, the study will include a 6-month follow-up period, including 6 telephone and survey visits, with no in-person visits. During the COVID-19 pandemic, visits that can be conducted remotely (screening visit) will be conducted virtually.

4.5 Total Number of Subjects and Sites

It is expected that approximately 80 subjects will be consented/enrolled at Penn in order to produce 40 evaluable subjects in total (due to missing data, drop out, etc.).

4.6 Vulnerable Populations:

No children, pregnant women, fetuses, neonates, or prisoners are included in this research study.

5 Study Intervention (Study drug, device, biologic, vaccine, food etc.)

5.1 Description

Transcranial Magnetic Stimulation (TMS) is a non-invasive form of brain stimulation. TMS can influence activity in various brain regions, and it allows researchers to test or modify brain circuit communication. This study will employ the following investigational devices:

- MagPro X100* magnetic stimulator
- Cool-B65 Butterfly Coil

The MagPro X100* magnetic stimulator and Cool B-65 Butterfly Coil are both approved devices for rTMS treatment of MDD.

5.2 Intervention Regimen

TMS will be administered in theta-burst stimulation (TBS; Huang et al., 2005), which involves triplets of TMS pulses at 50Hz, with intermittent breaks. The intermittent TBS (iTBS) protocol involves 40 trains of 10 TMS triplets, and each train is followed by an 8 second pause. Therefore, each TBS session is administered in a 7-minute block for a total of 1200 stimulations. Subjects then have an approximate 20-minute break before a second 7-minute block of iTBS resumes. Therefore, each stimulation session will involve <3700 stimulations. Stimulation sessions will take place over 10 consecutive weekdays. All subjects will receive iTBS for 10 consecutive weekdays at both target sites as a part of the study. After the first set of 10 stimulation sessions, subjects will have a 3-week break before returning to the laboratory for iTBS administered over an additional 10 consecutive weekdays.

The iTBS in this study will take place at two locations. One site, the DLPFC, is the standard site for TMS treatment. This site is determined by taking scalp measurements and targeting the region 6 cm anterior to motor cortex in a parasagittal line. Targeting for a second site in this study, a sub-region of the DLPFC that we refer to as the fMRI-guided target or LPFC, involves the use of a prior MRI scan to determine the site of stimulation. Structural MRI data will be used to specifically identify the LPFC on each individual's brain. Functional MRI data will further specify the exact location of stimulation, as the precise target for stimulation will be region that demonstrates the greatest activity during functional MRI scanning.

5.3 Storage

All interventional devices are owned, stored, and managed by the Center for Neuromodulation in Depression and Stress (CNDS). All devices are stored behind locked doors with restricted access to members of the CNDS. These devices are located at the CNDS lab-space in the Richards Biomedical Building.

5.4 Blinding

The administering clinician will be blinded as a part of this study. All subjects will receive TMS to both stimulation sites (fMRI-guided target/ DLPFC) as a part of this study in 2-week intervals. The order of site of stimulation is randomized and counterbalanced.

5.5 Administration and Accountability

Staff will be trained on the protocol and inclusion/exclusion criteria. TMS protocols will be administered by specially-trained staff in the CNDS. All TMS staff will be trained by the PI (Desmond Oathes, Ph.D.) and the Center Director (Yvette Sheline, M.D.). These procedures are in accordance with the "Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research" (Rossi et al., 2009). MRI scans will be conducted by MRI technologists trained at the Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS).

6 Study Procedures

Procedure	Screening (2-3 Hours)	Baseline (2-3 Hours)	TMS Treatment (1 ½ hours)	*3 week break* 2 Phone calls (30-60 minutes)	TMS Treatment (1 ½ hours)	Follow-Up Calls (30-60 minutes)
Visit Number	**0**	**1**	**2-11**	**N/A**	**13-22**	**N/A**
Visit Type	In-person (Virtually during COVID-19)	In-person	In-person	Phone	In-person	Phone/ Surveys
Study Duration	2-3h	2-3h	1-2h	30min	1-2h	30min
Informed Consent	X					
Clinical Assessments	X	X	X	X	X	X
Neurocognitive Assessments		X	X (Visit 11 Only)		X (Visit 22 Only)	
MRI		X				
TMS	X (Demonstration Only)		X		X	
Behavioral Tasks			X		X	
EEG and eyetracking		X	X (Visit 11 Only)		X (Visit 22 Only)	

***Visit 11 and Visit 22 may take up to 2 hours to complete
During the COVID-19 pandemic the screening visit and other procedures may be completeled remotely.

Does your study use MRI? (CAMRIS is the appropriate contact for all studies involving MRIs)

☒ Yes ☐ No

Check of all that apply:

☐ 1.5T MRI
☒ 3T MRI
☐ 7TMRI

Does the MRI use investigational sequences and/or coils?
(See Experimental Device Clause)

☒ Yes ☐ No ☐ Unsure (if unsure you need to contact CAMRIS)

Does your study include pregnant women?
(See Pregnancy Clause and Justification)

☐ Yes ☒ No

Does the MRI require the use of Contrast Agents?
(See Contrast Risks)

☐ Yes ☒ No

Does your study involve the exposure to radiation, radiotracers and/or radiological imaging modalities?

☐ Yes ☒ No (If No, no RRSC review is needed)

Will any of the radiation exposure result from procedures that are or could be performed solely as a result of a subject's participation in the research protocol?

☐ Yes ☒ No

Ultrasound

☐ Yes ☒ No

Will your study be using CT Scans? (CACTIS is the appropriate contact for studies involving CT scans)

☐ Yes ☒ No

Check off all of the following procedures that will be performed in your research- each option you select will link to the template language document:

☐ Apheresis/plasma exchange
☐ Leukapheresis
☐ Bone Marrow Biopsy or Aspirate
☐ Use of AP clinical specimens
☐ Biopsies- check those which apply
☐ Blood draw

6.1 Screening

Prior to any study visits, all subjects will be screened in a telephone interview with a trained member of the study staff or complete a self-report screening survey.

Those who pass the screen will receive an appointment to come to the research location to review the informed consent form and conduct the baseline diagnostic assessment screen to determine eligibility. Informed consent will be obtained upon arrival at this initial visit and before any study-related procedures are conducted. All subjects will have the opportunity to ask questions before signing a consent form. The rest of this initial visit will be an extended screening, which includes a structured diagnostic interview, psychiatric and medical evaluation, and collection of demographic information. Subjects will undergo a short demonstration of TMS to ensure that they are comfortable with all study procedures. This process involves adjusting the TMS device to a moderate level of stimulation and administering single pulses to the prospective TMS sites. A structured interview, *Diagnostic and Statistical Manual of Mental Disorders - DSM-5* will be used to assess the DSM criteria for PTSD or trauma induced MDD and the PHQ-9 will be used to assess presence of depressive symptoms. If subjects have time limitations, we may provide the option to complete the some of these assessments remotely (by phone/ sending the surveys) or to split the visit in two visits. Additionally, during the COVID-19 pandemic, the screening visit will be conducted virtually. If any of these adjustments are made, we will make a note in their records. For participants that indicated regular drug use in prescreening or screening forms, we may use a urine drug screen to confirm adherence to study policy of abstinence. The urine drug screen will be collected by study staff; test results will be stored in REDCap and the test destroyed immediately after.

6.2 Study Intervention Phase

6.2.1 Visit 1 (sometimes referred to as the baseline visit)

Visit 1 (aka Baseline) will take approximately 2-3 hours. If participants have time limitations, we may provide the option to complete the clinical assessments remotely (by phone/ sending the surveys) or to split the visit in two visits. If any of these adjustments are made, we will make a note in their records. At the first study session, subjects will complete 60 minutes of structural MRI and resting-state fMRI scans. Structural and functional scans will be obtained in each session on a clinically-approved 3 Tesla Siemens Prisma (Erlangen, Germany) scanner, equipped with 40mT/m gradients and 200 mT/m/s slew-rates. RF transmission will use a quadrature body-coil, and reception will use a Siemens receive-only 64-channel head coil. The total time in the scanner will be approximately 60 minutes. An experienced technician and a member of the study team will be present during the MR session to ensure participant safety and well-being.

Additionally, clinical assessments of thoughts, mood, and behaviors will be completed. Subjects will complete the following neurocognitive assessments during this visit:

i. Nback task: Computerized task to measure working memory capacity.
ii. Trails A & B task: Computerized task of visual attention and task switching.
iii. Stroop/Word task: Neurophysiological testing of cognitive interference.
iv. Foraging task: Computerized test to measure reward seeking behaviors.

In collaboration with Arjun Ramakrishnan from the Platt Lab, EEG data will be collected when the participants are engaged in the above-mentioned tasks. We may also record the location of their gaze at any particular time during these tasks using a passive eye-tracking device. The eyetracker will use a camera to identify the position of the pupil and cornea (using near-infrared reflection). By tracking the gaze of the subjects as they make decisions, we can obtain information about what subjects attended to during their decisions, for how long they attended to it, and in what order they attended to it.

6.2.2 Visits 2 - 11

Visits 2-11 are the first set of TMS treatment visits; each visit will take approximately 1 ½ to complete. If participants have time limitations, or during the COVID-19 pandemic, we may provide the option to complete the clinical assessments remotely (by phone/ sending the surveys) and we will make a note in their records. Brain data from the MRI scan (stimulation target in individualized brain space) will be calibrated with the skin and scalp using a Polaris Vicra camera (Brainsight neuronavigation) to allow marking of the stimulation sites. In addition, subjects will be evaluated to determine their motor threshold, or the amount of stimulation at the motor cortex needed to create an involuntary thumb twitch. This preparation time is expected to take approximately 30 minutes. Then, the TMS devices will be used to administer theta-burst stimulation (. TBS will be administered twice per session, with approximately a 20 minute break between each round of TMS. Participants will complete a short clinical assessment before and after each TBS session.

During the break between TMS rounds, participants will either complete a working memory task or watch a peaceful video;. These tasks are being added to the study protocol in order to activate brain areas through which the TMS treatments are expected to enhance relaxed mood (nature videos) or increase cognitive control (nback working memory task). Randomization will be by random number generator with eventual matching by demographics (age, race, gender) to balance the groups later in the study, as necessary.

During TMS, subjects will be asked to sit still for approximately seven minutes at a time when TBS is administered. The total number of stimulations in each TBS block is 1200 stimulations, for a total of 2400 stimulations. We approximate that the additional single pulses to determine motor threshold will not exceed 100 additional pulses. At the end of each TBS session, participants will complete additional clinical assessments. If participants have time limitations, we may provide the option to complete the clinical assessments remotely (by phone/ sending the surveys), and we will make a note in their records. TBS sessions are expected to take approximately 1 ½ hours, except for Visit #11 and visit #23 which will involve

additional clinical and neurocognitive assessments and will last approximately 2 hours During these neurocognitive assessments, we may collect EEG and eyetracking data, as in the Baseline Visit.
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We may use Neuroflow software for recording participants' heart rate during each TMS treatment session. NeuroFlow's software platform analyzes data from a commercially available, third-heart rate monitor. NeuroFlow follows strict HIPAA guidelines with respect to patient privacy and data security, both from a technical and administrative respective. Only de-identified data will be recorded using this platform, no identifiers will be entered on the platform.

Participants will have a 3 week break from TMS treatment between the first set of TMS sessions (i.e., Visit 2-11/Weeks 1 & 2) and the second set of TBS sessions (i.e., Visits 13-23/Weeks 6 & 7). During this time, participants will not be coming into the lab. However, participants will be scheduled for two phone/survey visits approximately one week, and two weeks (+/- 3 days) following Visit #11, in which clinical assessments will be completed.

Due to the nature of TMS treatment, daily visits are necessary. In the event a participant misses a session, the participant may complete two TMS treatment sessions on one day with ample time in between. In this case, the principal investigator will consider the timeline of missed sessions and evaluate how the missed sessions may be made up appropriately. If too many sessions are missed (as per PI discretion), the participant may be withdrawn from the study without their consent.

6.2.3 3 week break & Phone Calls

Participants will have a 3 week break from TMS treatment between the first set of TBS sessions (i.e., Visit 2-11/Weeks 1 & 2) and the second set of TBS sessions (i.e., Visits 13-22/Weeks 6 & 7). During this time, participants will not be coming into the lab. However, participants will be scheduled for two phone calls and Check-In surveys approximately one week (+/- 3 days) and two weeks (+/- 3 days) following Visit #11, in which clinical assessments will be completed.

6.2.4 Visits 13 - 22

Visits 13-22 are the second set of TMS treatment visits and will consist of identical procedures and will take the same amount of time as Visits 2-11, but stimulations occurring at the targeted site not used in the initial round of TMS treatments Please see sections 6.2.2 for further explanation on these visits.

6.2.5 6 Month Follow-Up: Phone Calls

Upon completion of the study, scheduled phone and survey visits will take place every 4 weeks (+/- 7 days) over the subsequent 6-month period to monitor continued stability of clinical improvement and/or remaining clinical symptoms. Each phone and survey visit will include clinical assessments and will take approximately 30-60 minutes.

6.3 Subject Withdrawal

Subjects may withdraw from the study at any time. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention, study procedures, or visit schedule. The Investigator or the Sponsor (if applicable) may also withdraw subjects who violate the study plan or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the study. No tapering procedure with TBS is necessary or required in the event that a subject withdraws from this study.

6.4 Pregnancy Testing

Consistent with clinical care standards for MRI scanning, attestation of pregnancy status will be accepted at the time of MRI screening. In addition, attestation of pregnancy status will be requested prior to TMS treatment.

6.5 Other Evaluations, Measures

During the course of the study, patients' symptoms will be evaluated in order to determine changes in symptoms across the study. Symptom scales are detailed below in the "Efficacy Evaluations" section.

6.6 Efficacy Evaluations

The following clinical assessments will be utilized at baseline, after the first 2-week period of TMS treatment, during the TMS treatment 3 week break, and after the second 2-week period of TMS treatment (the end of the study) to evaluate the efficacy of the TMS interventions in improving clinical symptoms:

- Patient Health Questionnaire (PHQ-9)
- PTSD Checklist for DSM-5 (PCL-5)
- Montgomery-Asberg Depression Scale (MADRS)
- Columbia Suicide Severity Rating Scale (CSSRS)
- Positive and Negative Affect Schedules (PANAS - 20 item)
- World Health Organization Quality of Life (WHOQOL-BREF)
- Snaith-Hamilton Pleasure Scale (SHAPS)

6.7 Safety Evaluations

Only individuals trained by the Principle Investigator (Desmond Oathes, Ph.D.) and Center Director (Yvette Sheline, M.D.) will dispense TMS. The licensed physician (Sheline, M.D. or a suitable medically trained stand-in) will closely supervise any medical instability in patients and will specifically be responsible for training and overseeing syncope and seizure management which are not expected given our screening process but are the two primary health risks with TMS treatment.

Dr. Sheline, a board certified physician, will review all questionable screens for MRI and TMS safety and will be physically present (or a reasonable medically trained stand-in) for every TMS session conducted on any participant who indicates greater than minimal risk for experiencing syncope or a seizure in response to TMS.

Only research personnel will have keys and access to the TMS devices.

7 Statistical Plan

All recruitment will be conducted through the University of Pennsylvania, the Veterans Administration Medical Center, and surrounding community to find 80 patients with PTSD or trauma induced MDD and depressive symptoms. It is anticipated that a large portion of individuals will screen fail, withdrawal from participation or have unusable data. Therefore, 80 individuals will be consented/enrolled in this study, to ensure that there are 40 patients who complete the full protocol with usable data. This sample should provide us with adequate data to compare treatment sites relative to one another, since all patients will receive the standard targeting for TMS and also fMRI-guided TMS.

7.1 Primary Endpoint

The primary endpoint of this study will be clinical improvement due to TMS performed at either the standard brain target or the fMRI-guided brain target.

7.2 Secondary Endpoints

The secondary endpoint of this study will be the correlation between resting-state connectivity prior to TMS and the degree of clinical change in response to TMS treatment targeting each circuit.

7.3 Sample Size and Power Determination

Using an effect size (Hedge's g) calculated from published work doing theta burst stimulation treatment for MDD to a nearby brain area (dorso-medial prefrontal cortex) in a sample of 87 patients and yielding an effect size of 1.225 (% improvement, Hamilton Depression scale), a priori power analysis (Power 0.80, p-

value 0.05) indicates that we will need at least 6 patients to generate a significant change in symptoms which is well below our planned enrollment.

7.4 Statistical Methods

The primary analysis will be a Site x Time ANOVA on the Hamilton Depression rating scale comparing pre-treatment to symptoms immediately following each round of stimulation. This test will be augmented by a Site x Time ANOVA for pre-treatment compared with the 6 month timepoint to explore the degree of maintenance of treatment benefits.

7.4.1 Baseline Data

After 10 participants are randomly assigned to each stimulation order, an analysis of demographic data (age, education, gender, symptom severity) will address any initial differences in baseline characteristics of the two samples. If there is a systematic difference, randomization will be temporarily suspended to assign patients to one or other of the two groups in order to re-balance the initial baseline characteristics of the two groups. [Independent samples t-tests for continuous variables and Chi-square for categorical variables]

7.4.2 Efficacy Analysis

Efficacy analyses will focus on comparisons between clinical symptoms at baseline, after the first 2-week treatment period, and at the end of the second 2-week treatment period. As noted above, the primary endpoint of this study will be a comparison focusing on clinical improvement due to TMS performed at either the standard brain target or the fMRI-guided brain target.

7.4.3 Interim Analysis

After the first 12 participants are run for each protocol, the study team will evaluate the overall rate of change in symptoms. If less than one quarter of participants experience at least a 25% reduction in Hamilton Depression scores, the team will consider a change in stimulation protocol or target. Safety and tolerability will also be assessed at this interval and if the team decides that the procedures are safe and appropriate, enrollment will continue up to 60 participants.

7.4.4 Safety Analysis

All subjects entered into the study will have detailed information collected on adverse events throughout the study duration, and this information will be used for the overall study safety analysis. These factors will include: worsening of symptoms, development of new psychiatric symptoms, medical effects (syncope, seizure, or other), and any equipment failures.

7.5 Subject Population(s) for Analysis

All data collected from enrolled subjects, who meet the eligibility criteria and complete, at minimum, baseline assessments will be analyzed. In the event that a subject does not complete the full study, their completed time-points may still be used in analyses, such as characterizing baseline fMRI activity and symptom severity. Any subjects enrolled into the study and meeting the eligibility criteria, regardless of whether they received investigational product, may be included in these analyses.

8 Safety and Adverse Events

8.1 Definitions

8.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that the Principal Investigator determines as significantly worse during course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event

- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

For FDA regulated studies the FDA defines an adverse event as the following:

Adverse event means any untoward medical occurrence associated with the use if a drug in humans whether or not considered drug related.

8.1.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that 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

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.

8.2 Recording of Adverse Events

The PI will monitor the study for any serious and adverse events. All serious events (SAE) will be reported to the IRB: a) Death: immediately b) Life-threating and all other SAEs within 7 calendar days. Should there be a serious event that occurs that increases the risks to the participants the study will be stopped, an investigation will be conducted, and a findings report will be generated before the study is resumed.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

8.3 Relationship of AE to Study

The relationship of each adverse event to the study procedures will be characterized. The PI will determine the relationship of each adverse event to the study procedures and how that relationship will be classified (definitely related, probably related, possibly related, unlikely, or unrelated).

8.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

This study will comply with the Penn IRB definition of reportable events and reporting timelines. The investigators and the protocol sponsor will conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible. Additionally all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints will be recorded and reported with respect to institutional and federal policies as described in the Penn Manual.

8.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

8.4.2 Investigator reporting: notifying the study sponsor

Any study-related unanticipated problem posing risk to subjects or others, and any type of serious adverse event, will be reported to the study sponsor by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form will be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site.

Within the following 48 hours, the investigator will provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor.

8.4.3 Investigator Reporting: Notifying the Penn IRB

In compliance with the University of Pennsylvania reporting requirements and timelines, the principle investigator (Dr. Oathes) will submit reports within 10 working days of discovery (with one exception) for events that meet reporting criteria. If the adverse event involved a death and indicates that participants or others are at increased risk of harm, the investigator will submit a report to the IRB within 3 days. In the event that the investigator does not have enough information to complete the Reportable Event form within this timeframe, he will still submit a Reportable Event Form. In such cases, a follow up report will be provided once additional information has been obtained.

8.4.4 Sponsor reporting: Notifying the FDA (applies only to Penn sponsor –investigator IND/IDE holders)

To be determined.

8.5 Medical Monitoring

Dr. Sheline, a board certified physician, will review all questionable screens for MRI and TMS safety and will be physically present (or a reasonable medically trained stand-in) for every TMS session conducted on any participant who indicates greater than minimal risk for experiencing syncope or a seizure in response to TMS which are the primary medical risks for this procedure. It is the responsibility of the Principal Investigator to oversee the safety of the study in collaboration with Dr. Sheline and other collaborating medical staff. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above.

Participants will meet the clinician treating them at each TMS treatment visit where they also report on their current symptoms. During the 3 week break, we also call them to assess symptom changes. Substantial worsening of symptoms to the point of potential threat determined by the study physician (Sheline) and PI (licensed psychologist) will result in a threat assessment of the patient which, depending on the degree of worsening, will facilitate: brief de-escalation interventions, request for self-admit to nearest emergency room, request for family/friend accompaniment to ER, or a call to emergency services for patient pick up. The procedures are all done within walking distance of the Department of Emergency Medicine at Penn Medicine, which will be the first choice for emergency services if the patient is ambulatory and willing to accompany study staff to the hospital. The VA hospital is also within walking distance and will be the preferred ER for veteran participants.

If the patient endorses a significant worsening of symptoms that is abnormal for their typical illness course or puts them into a category of imminent risk for self-harm, their participation will be discontinued.

8.5.1 Data and Safety Monitoring Plan

Monitor Selection: One monitor will be assigned for this study and will be responsible to complete the monitoring process. The monitor will be a research coordinator at the center who is not the lead research coordinator for this study. An updated CV will be kept on file in the Research Personnel regulatory binder to document the qualifications of the monitor.

Data Management: All data will be de-identified and only qualified research personnel will be have access. Records will be kept electronically on password-protected servers.

Safety Monitoring: All unanticipated problems will be reported to the Principal Investigator or delegated research staff for the duration of the study. The Principal Investigator has the front-line responsibility for identifying potential adverse events experienced by study participants, making adjustments accordingly, and reporting the experience. The P.I. is responsible for tracking these reports and relaying them as required to the IRBs and other investigators. Data integrity, safety, and privacy will be monitored by the PI and the coordinators.

The following activities will be completed by the monitor to close out the study:

- Ensure all data has been reviewed and collected;
- Confirm all reports of unanticipated problems have been reported to the IRB(s);
- Review the regulatory documentation and subject files for completeness and compliance with all applicable federal regulations;
- Ensure that all continuing review reports were submitted to and approved by the IRB(s);
- Review requirements for record retention with the investigator and the clinical staff.

The checklist will be signed by the monitor and included in the regulatory files.

8.5.2 Data Safety Monitoring Board

This study will not require a DMC or DSMB.

9 Study Administration, Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Data Collection and Management

Staff will be trained on the protocol and inclusion/exclusion criteria. Other facilities will include various laboratory spaces specializing in advanced computing and analysis of neuroimaging and cognitive datasets.

Structural and functional scans will be obtained in each session on a clinically-approved 3 Tesla Siemens Prisma (Erlangen, Germany) scanner housed in the Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS), equipped with 40mT/m gradients and 200 mT/m/s slew-rates. RF transmission will use a quadrature body-coil, and reception will use a Siemens receive-only 64-channel head coil. The total time in the scanner will be approximately 60 minutes. All MRI imaging will be reviewed and approved by CAMRIS. Additional MRI resources, such as a mock scanner, may be accessed from the Center for Functional Neuroimaging (CfN).

Patients entering the study will be given a unique identifying code. This code will be used on all data obtained from scans or the medical record. Only one password protected document connecting the code

with the participant name will exist. This subject key will be maintained on the University of Pennsylvania's secured server (aka, PMACS); only the research coordination team will have access to this key and a record will be kept of all personnel who have been granted access. All collected data will be immediately coded and this coded information will be stored in secure cabinets inside locked rooms or in password protected, IRB compliant online databases, such as REDCap. All data will be deidentified and only qualified research personnel will be have access. Records will be kept electronically on password protected servers. Deidentified information may be shared with collaborating researchers within the University of Pennsylvania and at collaborating institutions. This information will be stripped of all personal health information (PHI) and other personal identifiers.

9.3 Records Retention

Records from collected data will be kept in locked cabinets in the CNDS facility accessible only to study staff for 7 years following the completion of the investigation.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The PI will be responsible for personnel training and for responding to adverse events. The study physician will oversee training to address and respond to the two most common medical consequences of TMS administration (syncope / seizure). The safety monitor will be given review space and access to study documents including symptom scales recorded during the investigation. In the event of any reported medical consequence more severe than a mild temporary headache, all of the study staff including the study physician (Dr. Sheline) will meet to review patient records and reports to evaluate whether safety monitoring should be increased and/or whether study procedures should be changed to minimize risk for participants. The study physician will also telephone the participant to discuss possible contributors to the medical consequence, to evaluate the severity of persistent symptoms, and to recommend follow up care, if warranted.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

11.1 Risks

There is a small risk of loss of confidentiality.

Clinical Interview and Assessment: Some discomfort may be associated with the clinical assessments conducted in this study. Participants may experience emotional discomfort when answering some questions

in the questionnaires or when talking about personal information. Participants may choose not to answer any of the questions and to terminate their participation.

MRI scan: Likely/Common: Subjects may experience claustrophobia (fear of enclosed spaces and/or anxious feelings accompanied by fast heart rate or shortness of breath) within the MRI scanner. In addition, the scanner produces a loud repetitive knocking noise during the study that some people find bothersome. If a subject has a problem with feeling uncomfortable while inside the scanner, they may stop this study. To lessen the noise, earplugs will be provided.

Rare: Implanted medical devices and metallic foreign fragments inside the body may pose a risk if a subject were to enter the MRI magnet room. Devices such as Pacemakers, Internal Cardiac Defibrillators, Insulin Pumps, and other medical devices may also prevent a safe MRI. Therefore, questions regarding medical and work history will be asked prior to your exam. Patients who have metallic devices in their bodies will not be permitted to be scanned using MRI. There are no known risk factors associated with MRI scans for healthy subjects. 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.
Consistent with clinical care standards for MRI scanning, attestation of pregnancy status will be accepted at the time of MRI screening. Some people may find the MRI to be uncomfortable and claustrophobic. Participants will be instructed to inform the doctor ordering the scan, or the study staff, if they suffer from claustrophobia. The MRI scanner produces different types of noises during a scan. Since the noise level can be loud, participants may be given special earplugs to reduce the noise. A MRI scanner has a strong magnet which attracts certain metals. If anyone has these types of metal in their body, the MRI's strong magnetic field can cause them to move which may cause injury. The MRI will not be performed on anyone having these types of metal in their body. To prevent an injury, participants will be asked questions or given a form requesting information about any metal in their body and if they work with metals. Some dyes in tattoos and permanent eyeliner contain metals which may move during the MRI scan causing the area with the tattoo to become irritated and swollen. No metal objects are allowed to be brought into the MRI scan room at any time, because the MRI magnet will quickly and strongly pull those items into the scanner. To prevent any injury to patients and staff and any damage to the MRI scanner, participants will be asked to remove all jewelry and clothing containing metal before you enter the MRI scan room. Also, since the MRI magnet will erase credit cards, they must not be taken into the scan room. Once participants are positioned in the scanner, the door to the room will be closed to prevent anyone with any metal object entering the scan room.

TMS: TMS is considered to be a low-risk procedure. The only common side effect of TMS (approx 25% of patients) is a mild headache. There are no known significant risks with this procedure at this time because the magnetic fields at the strengths used are thought to be without harm. For a normal healthy person, producing a seizure from TMS in this experiment is very unlikely. There has been only one reported seizure in the history of theta-burst stimulation studies (Rossi et al., 2009). There are no known long-term adverse effects reported with the use of this device. Rarely, device malfunction could result in a scalp burn. There may be unforeseen risks in the long-term that are currently unknown. The TMS device produces a clicking sound. Although studies have found no hearing impairments as a result of this sound, some subjects experience a mild temporary effect on their hearing. To minimize this possibility, subjects will be given protective earplugs or headphones.

EEG: The EEG procedures are safe and have been in use for decades in both clinical and basic research settings. There are no known major risks associated with this procedure. Some people may experience a mild headache or discomfort when wearing the headset and completing the computerized tasks. Very rarely, seizures have been reported during EEG recordings for individuals with a preexisting condition of seizure disorder. Subjects who experience any discomfort will be encouraged to withdraw from the EEG component of the study. Subjects with a known history of seizures are not be eligible for the study.

Eyetracking device: The eyetracking device feels and looks like regular eye glasses. Subject can move their eyes, head, and body as normal. No discomfort is expected during the procedure.

11.2 Benefits

There is no promise of benefit to subjects in this study. MDD/PTSD subjects may benefit by a reduction in symptoms from treatment with TBS. There is no benefit for receiving the MRI scans or for the clinical assessments. The scans and the clinical assessments are performed only for research, and the results are not routinely shared with participants. However, in the event that clinically significant MRI abnormalities are discovered, subjects will be informed of the finding and referred to their physician. An indirect benefit of participating in this study is contributing to scientific knowledge. This study has the potential to greatly increase our knowledge of treatment mechanisms in people with MDD/PTSD and may lead to new treatment standards in the future.

11.3 Risk Benefit Assessment

This study is minimal risk. There is essentially zero risk of harm from the research procedures (MRI, TMS, EEG, eyetracking device, assessments of symptoms). The potential individual benefit from the study treatments, and the potential benefits to society through the increased understanding of treatment methods in MDD/PTSD, outweigh the potential risk from the MRI and TMS procedures. Additionally, those who would be unable to tolerate TMS or an MRI scan will be screened out.

11.4 Informed Consent Process / HIPAA Authorization

Prior to any study visits, all subjects will verbally consent to a telephone screening interview with a trained member of the study staff. Informed consent will be obtained upon arrival by a qualified research coordinator before any study-related procedures are conducted. This consenting process will take place in a private room at the CNDS lab-space at the University of Pennsylvania to protect the patients' privacy. All subjects will be reminded to ask questions before signing a consent form, and all subjects will receive a copy of the signed consent form to keep for their own documentation.

11.4.1 Alterations to Typical Consent Process (only include if applicable)

11.4.1.1 Waiver of Consent (In some cases for screening/portions of that study that qualify as minimal risk, a waiver of documentation of consent may be permissible per IRB SOPs)

This study will involve a waiver of documentation of consent for the telephone screening procedure in this protocol. This waiver will permit coordinating study staff to conduct a telephone screening interview with potential research subjects prior to any study visits.

This process involves no more than minimal risk to the subjects. In addition, the waiver or alteration will not adversely affect the rights and welfare of the subjects. Furthermore, the research could not practicably be carried out without this waiver or alteration. Finally, whenever appropriate, the subjects will be provided with additional pertinent information after participation.

12 Study Finances

12.1 Funding Source

This study is financed through a grant from CureAccelerator (Cures Within Reach) and the Kahlert Foundation. Additional support (co-funding) will be provided by the University of Pennsylvania School of Medicine.

Compensation for the EEG and eyetracking procedures of this study, done in collaboration with Arjun Ramakrishnan, is funded separately through Dr. Ramakrishnan's grant (the 2018 NARSAD Young Investigators Grant, grant number 27649).

12.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

12.3 Subject Stipends or Payments

Subjects will receive $30 for completion of the MRI procedure. All TMS treatment is free to patients as a part of the study. During the Baseline, Visit #11 and Visit #23 if participants complete the EEG and eyetracking recording procedure, they will receive a total of 75$ (25$ per visit) at the end of the study. Therefore, subjects will receive a grand total of $105 if they participate in the EEG/eyetracking procedures and MRI. If subjects prefer not complete the EEG/eyetracking recordings, they will receive $30 for completing the MRI. We will provide these options in the Inform Consent Form.

If participants have already completed an MRI as a part of another study at our center, this MRI may be able to be used for this this study and may not need to be repeated. In this case, participants would not be compensated for the MRI scan.

Additionally, participants who request transportation assistance will receive up to $10.00 for travel for each visit.

Subjects will be compensated through University of Pennsylvania supported Greenphire ClinCard. This is a reloadable prepaid card (similar to a debit/credit card) which allows funds to be available immediately. Study staff will provide participants with a ClinCard Cardholder FAQ: US document (attached). Subjects will receive compensation at the end of their study completion. Subjects who do not feel comfortable with the Greenphire ClinCard may be compensated by a check, in lieu of the ClinCard. We are not stating this option in the ICF, as we would prefer all participants to use the ClinCard for consistency; however, we acknowledge that not all individuals will feel comfortable with this method and therefore, if during the consenting process or at any time during the study, a participant expresses discomfort, we will then verbally offer them the option of being paid with a check. We will add a note to file for each subject that receives compensation in the form of a check instead of a ClinCard.

13 Publication Plan

The sponsor has no limitations on how the data will be analyzed or published with the exception that their funding contribution be acknowledged. The PI holds the primary responsibility for publication of the results of the study.

14 References

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15 Attachments

There are currently no attachments included with this protocol.

16 Appendix

16.1 Devices

16.2 Studies Involving Research MRIs - CAMRIS Standard Language for a Protocol or Study Consent Form

16.3 Studies Involving Radiation, Radiotracers and/or Radiological Imaging Modalities (RRSC) Standard Language for a Protocol or Study Consent Form

16.4 Studies Involving Research CT Scans - CACTIS Standard Language for a Protocol or Study Consent Form

16.5 Studies Involving Nuclear Medicine Regulated Research Procedures

16.6 Research Studies Involving Pathology And Lab Medicine

16.7 Reference for Safety Reporting Section- Common Definitions for Developing and Adverse Event Tracking and Serious Adverse Event Reporting Protocol

16.8 Expedited FDA Reporting Requirements

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND/ IDE safety reports.

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- **Within 7 calendar days**
  Any study event that is all:
  - associated with the use of the study drug, and
  - unexpected, and
  - fatal or life-threatening,

- **Within 15 calendar days**
  Any study event that is:
  - associated with the use of the study drug, and
  - unexpected, and
  - serious, but not fatal or life-threatening

-or-

– a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

Any finding from tests in laboratory animals that:

– suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The following describes the IDE safety reporting requirements by timeline for reporting and associated type of event:

- **Within 10 working days**
  Any study event that is all:
  – associated with the use of the study drug, and
  – unexpected, regardless of the seriousness of the event.

- **Within 5 working days**
  – Protocol deviation to protect the life of the subject in emergency
  – Withdrawal of IRB approval
  – Lack of informed consent

Additional reporting requirements
Sponsors are also required to identify in IND/IDE safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Applicable events can be reported to the FDA using Form FDA3500A or in narrative format. The report must be sent to the correct division. Specific information that must be included in the reports can be found in 21 CFR 312.32 or in 21 CFR 812.150.

[Include the appropriate FDA Division, telephone number and fax number here]

16.9 DSMB Reference: The following section of guidance language draws from: the FDA Guidance Document: "Guidance for Clinical Trial Sponsors on the Establishment of Clinical Trial Data Monitoring Committees"

16.10 Source Documents

There are currently no source documents for this protocol.

16.11 Case Report Forms (CRFs)

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

16.12