MINI THETA BURST TMS IN MDD PATIENTS (NARSAD)

Last Update: 16 December 2020

Principal Investigator (1) Desmond J. Oathes, Ph.D.
Department of Psychiatry
Richards Biomedical Building D306
3700 Hamilton Walk
Philadelphia, PA 19104
215-573-9390
oathes@mail.med.upenn.edu

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

IRB Number: 825761

ClinicalTrials.gov Number NCT04014959

Protocol Details

Basic Info

Confirmation Number:	**dcibbebe**
Protocol Number:	**825761**
Created By:	**ROSENBERG, BENJAMIN**
Principal Investigator:	**OATHES, DESMOND J**
Protocol Title:	**Mini Theta Burst TMS to Promote Brain Plasticity Indexed by fMRI**
Short Title:	**Mini-TBS Probe**
Protocol Description:	**Transcranial Magnetic Stimulation (TMS) is a non-invasive form of brain stimulation. TMS can temporarily influence activity in various brain regions, and it allows researchers to test brain circuit communication. We are investigating a novel TMS targeting method using fMRI to guide the precise location of stimulation. We hypothesize that fMRI-guided TMS will be effective at probing and influencing brain activity.**
Submission Type:	**Biomedical Research**
Application Type:	**EXPEDITED Category 1**

Resubmission*
Yes

Hospital Sites
Will any research activities and/or services be conducted at a Penn Medicine affiliated hospital site?
No

Study Personnel

Principal Investigator

Name:	**OATHES, DESMOND J**
Dept / School / Div:	**10579 - PS-Center for the Neuroscience of Depression & Stress**
Campus Address Mail Code	**3309**
Address:	**Richards Biomedical Building D306** **3700 Hamilton Walk**
City State Zip:	**PHILADELPHIA PA 19104-6116**
Phone:	**215-573-9390**
Fax:	**215-573-0759**
Pager:	
Email:	**oathes@mail.med.upenn.edu**
HS Training Completed:	**Yes**
Training Expiration Date:	**01/25/2019**
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

Study Contacts

Name:	**SCULLY, MORGAN**
Dept / School / Div:	**10579 - PS-Center for the Neuroscience of Depression & Stress**
Campus Address Mail Code	**3309**
Address:	**RICHARDS BUILDING** **Floor 3**
City State Zip:	**PHILADELPHIA PA 19104-6085**
Phone:	**215-746-6751**
Fax:	
Pager:	
Email:	**mscull@pennmedicine.upenn.edu**
HS Training Completed:	**Yes**
Training Expiration Date:	**09/20/2019**
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**FIGUEROA-GONZALEZ, ALMARIS**
Dept / School / Div:	**10579 - PS-Center for the Neuroscience of Depression & Stress**
Campus Address Mail Code	
Address:	
City State Zip:	
Phone:	**215-573-4229**
Fax:	
Pager:	
Email:	**almaris.figueroa-gonzalez@pennmedicine.upenn.edu**
HS Training Completed:	**Yes**
Training Expiration Date:	
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

Other Investigator

Name:	**SHELINE, YVETTE I**
Dept / School / Div:	**10579 - PS-Center for the Neuroscience of Depression & Stress**
Campus Address Mail Code	**6021**
Address:	**3700 Hamilton Walk Richards 301**
City State Zip:	**Philadelphia PA 19104-6019**
Phone:	**215-573-0082**
Fax:	**215-573-0759**
Pager:	
Email:	**sheline@pennmedicine.upenn.edu**
HS Training Completed:	**Yes**
Training Expiration Date:	**07/01/2019**
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

Responsible Org (Department/School/Division):

10579 - PS-Center for the Neuroscience of Depression & Stress

Key Study Personnel

Name:	**SEILHEIMER, ROBERT**
Department/School/Division:	**PS-Psychiatry**
HS Training Completed:	**Yes**
Training Expiration Date:	
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**CRISTANCHO, MARIO**
Department/School/Division:	**PS-Psychiatry**
HS Training Completed:	**Yes**
Training Expiration Date:	**02/21/2019**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**DELUISI, JOSEPH**
Department/School/Division:	**PS-Center for the Neuroscience of Depression & Stress**
HS Training Completed:	**Yes**
Training Expiration Date:	**04/15/2022**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**MURPHY, ANDREW**
Department/School/Division:	**Health System**
HS Training Completed:	**Yes**
Training Expiration Date:	**05/03/2019**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**JASKIR, MARC**
Department/School/Division:	**PS-Center for the Neuroscience of Depression & Stress**
HS Training Completed:	**Yes**
Training Expiration Date:	
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**SYDNOR, VALERIE J**
Department/School/Division:	**SM-DN-Biomedical Graduate Studies**
HS Training Completed:	**Yes**
Training Expiration Date:	**08/26/2021**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**DUPRAT, ROMAIN J**
Department/School/Division:	**PS-Center for the Neuroscience of Depression & Stress**
HS Training Completed:	**Yes**
Training Expiration Date:	**06/14/2020**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**STOCK, JANET**
Department/School/Division:	**PS-Center for the Neuroscience of Depression & Stress**
HS Training Completed:	**Yes**
Training Expiration Date:	**11/26/2020**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**HALEWICZ, VICTORIA**
Department/School/Division:	**Psychology**
HS Training Completed:	**Yes**
Training Expiration Date:	**08/22/2022**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**PEREZ, GIANNA**
Department/School/Division:	**SM-DN-Biomedical Graduate Studies**
HS Training Completed:	**Yes**
Training Expiration Date:	
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**MAKHOUL, WALID**
Department/School/Division:	**PS-Center for the Neuroscience of Depression & Stress**
HS Training Completed:	**Yes**
Training Expiration Date:	**09/03/2021**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**LIANG, XIMO**
Department/School/Division:	**PS-Center for the Neuroscience of Depression & Stress**
HS Training Completed:	**Yes**
Training Expiration Date:	**06/21/2022**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Disclosure of Significant Financial Interests*
Does any person who is responsible for the design, conduct, or reporting of this research protocol have a **FINANCIAL INTEREST**?
No

Penn Intellectual Property*
To the best of the Principal Investigator's knowledge, does this protocol involve the testing, development or evaluation of a drug, device, product, or other type of intellectual property (IP) that is owned by or assigned to the University of Pennsylvania?
No

Certification
I have reviewed the *Financial Disclosure and Presumptively Prohibited Conflicts for Faculty Participating in Clinical Trials* and the *Financial Disclosure Policy for Research and Sponsored Projects* with all persons who are responsible for the design, conduct, or reporting of this research; and all required Disclosures have been attached to this application.
Yes

Biomedical Research

Clinical Trial*
Is this a clinical trial?
Yes

If Yes, please be aware that for each clinical trial conducted or supported by a Federal department or agency, one IRB-approved informed consent form used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal Web site that will be established as a repository for such informed consent forms.

Investigator Initiated Trial*
Is this an investigator initiated trial?
No

Drugs or Devices*
Does this research study involve Drugs or Devices?
Yes: Investigational devices that may qualify as Non-Significant Risk.

IND Exemption

For studies that fall under an IND exemption, please provide the number below

For studies including IND or IDE's, please provide the number(s) below

IDE Review*
NOTE: For research involving investigational devices, you are required to review the guidance on Managing Research Device Inventory. Consult the Penn Manual for Clinical Research: https://www.med.upenn.edu/pennmanual/secure/investigational-product-management-at-sites-not-using-investigational-drug-services-(ids).html Please check the box Yes if you have reviewed the guidance.
Yes

Research Device Management*
Please indicate how research device(s) will be managed.
The device receipt, storage and dispensing is being conducted by the research team (please provide information in the protocol summary as to how this will be conducted)

Drug, Herbal Product or Other Chemical Element Management *
Please indicate how drugs, herbal products or other chemical entities will be managed.
Not Applicable (no drugs, herbal products or other chemical entities)

Radiation Exposure*
Are research subjects receiving any radiation exposure (e.g. X-rays, CT, Fluoroscopy, DEXA, pQCT, FDG, Tc-99m, etc.) that they would not receive if they were not enrolled in this protocol?
No

Gene Transfer*
Does this research involve gene transfer (including all vectors) to human subjects?
No

Human Source Material*
Does this research include collection or use of human source material (i.e., human blood, blood products, tissues or body fluids)?
No

CACTIS and CT Studies*
Does the research involve Center for Advanced Computed Tomography Imaging Services (CACTIS) and CT studies that research subjects would not receive if they were not part of this protocol?
No

CAMRIS and MRI Studies*
Does the research involve Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS) and MRI studies that research subjects would not receive if they were not part of this protocol?
Yes

Investigational Agent or Device within the Operating Room*
Does the research project involve the use of an investigational agent or device within the Operating Room?
No

Cancer Related research not being conducted by an NCI cooperative group*
Does this protocol involve cancer-related studies in any of the following categories?
No

Processing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
No

In-House Manufacturing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
No

Medical Information Disclosure*
Does the research proposal involve the use and disclosure of research subject's medical information for research purposes?
Yes

If the answer is YES, indicate which items is is provided with this submission:

Modified research informed consent document that incorporates HIPAA requirements

CTRC Resources*
Does the research involve CTRC resources?
No

Pathology and Laboratory Medicine Resources*
Will samples be collected by hospital phlebotomy and/or processed or analyzed by any of the clinical laboratories of the University of Pennsylvania Health System?
No

Research Involves Apheresis, Cell Collection, and/or Blood Product Collection*
Does this research involve collection of blood products in the Penn Donor Center and/or the use of apheresis for treatment or collection of cells or other blood components?
No

Research involving blood transfusion or drug infusions*
Will your research involve blood transfusion or infusion of study drug in 3 Ravdin Apheresis Unit for research purposes?
No

Trial in Radiation Oncology
Is this research a prospective trial being done in Radiation Oncology, and if so, has this protocol been approved by the Radiation Oncology Protocol committee?
N/A

Study in Radiation Oncology
Is this research a retrospective study being done in Radiation Oncology, and if so, has this project been reviewed by the Radiation Oncology Clinical Research Group?
N/A

Use of UPHS services*
Does your study require the use of University of Pennsylvania Health System (UPHS) services, tests or procedures*, whether considered routine care or strictly for research purposes?
No

Primary Focus*
Other

Protocol Interventions

	Sociobehavioral (i.e. cognitive or behavioral therapy)
	Drug
	Device - therapeutic
	Device - diagnostic (assessing a device for sensitivity or specificity in disease diagnosis)
	Surgical
	Diagnostic test/procedure (research-related diagnostic test or procedure)
	Obtaining human tissue for basic research or biospecimen bank
	Survey instrument
x	**None of the above**

The following documents are currently attached to this item:

There are no documents attached for this item.

Department budget code

None

Multi-Center Research

Penn as lead
1. Is this a multi-center study where Penn is serving as the Lead Site or the Penn PI is serving as the Lead Investigator?
No

Management of Information for Multi-Center Research

Penn irb of record
2. Is this a multi-center study where the Penn IRB will be asked to serve as the IRB of Record for other external study sites?
No

Other Sites

No other sites

Protocol

Abstract
Non-invasive transcranial magnetic stimulation (TMS) is now FDA-approved for the treatment of major depressive disorder (MDD). However, there is growing evidence that the targeting strategy for

delivering TMS treatment would yield superior clinical outcomes if it were more tailored to individual neuroanatomy. In this study, we plan to examine whether functional MRI-guided TMS might be effective at temporarily influencing neural circuit communication. If this is true, future studies may utilize these methods to yield an even greater leap forward in promoting optimal clinical outcomes using full doses of TMS for treatment.

Objectives

Overall objectives
We aim to establish the efficacy of TMS stimulation at probing and temporarily influencing brain activity using targets defined by resting connectivity in MDD patients. We hypothesize that fMRI-guided TMS will be effective in modulating the connectivity of neural circuits.

Primary outcome variable(s)
Functional brain activity due to TMS performed at an fMRI-guided brain target

Secondary outcome variable(s)
Changes in functional brain activity after the 3 day stimulation regimen

Background
The subgenual Anterior Cingulate Cortex (sgACC) has been well established as a brain area sensitive to negative mood inductions and is 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 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 study will utilize individualized targeting from participants' own fMRI scans. We will focus on a target region of the lateral prefrontal cortex (LPFC) that our data suggest is particularly effective at influencing the sgACC. As alternative brain targets, we will also test the efficacy of prefrontal sites with hypothesized connections to downstream depression-related abnormalities. A normal, 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 TMS. We will be administering brain stimulation in smaller doses as compared with the FDA-approved protocol, but using a well-validated protocol, theta-burst stimulation (Huang et al., 2005), which will result in a reduced number of total pulses delivered to the subject in any given TMS session. This is not a treatment study, and stimulation is not designed to provide treatment in this study. Instead, the TMS delivery is meant to temporarily modify brain circuit communication between the lateral prefrontal cortex and subcortical structures to prove that this pathway can be influenced non-invasively with TMS. In addition to these repetitive TMS protocols, we will perform brief TMS delivery in the MRI machine with a research device (MRi-B91 Air Cooled Coil). 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 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 other protocols, 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.

Study Design

Phase*
Not applicable

Design
All subjects will receive active TMS to our novel fMRI-guided targeting method over the course of 3 days, preceded and followed by a 2hr MRI scan during which TMS is administered throughout.

Study duration
Enrollment of subjects in this study will take place over approximately 2 years. Each subject will complete 8 study visits over the course of ~3 weeks. The study schedule is as follows: Visit 1: Consenting / Screening procedures (approx. 3 hours) Visit 2: Baseline MRI Scan to determine TMS targets (1 hour) Visit 3: TMS/ fMRI Scan #1 & Assessments (approx. 3 hours) Visits 4-6: Mini TBS Visits - TMS to the fMRI-guided site (approx. 1hr each) Visit 7: Follow-Up Visit - TMS/fMRI Scan #2 (approx. 3 hours)

Resources necessary for human research protection
Describe research staff and justify that the staff are adequate in number and qualifications to conduct the research. Describe how you will ensure that all staff assisting with the research are adequately informed about the protocol and their research related duties. Please allow adequate time for the researchers to conduct and complete the research. Please confirm that there are adequate facilities for the research.
Staff will be trained on the protocol and inclusion/exclusion criteria. TMS protocols, as well as clinical and neurological assessments, will be administered by specially-trained staff in 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.). Other facilities will include various laboratory spaces specializing in advanced computing and analysis of neuroimaging and cognitive datasets. Scans will be conducted on a Siemens Prisma 3 Tesla whole-body MRI with a 64-channel head/neck array, housed in the Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS). Additional MRI resources, such as a mock scanner, may be accessed from the Center for Functional Neuroimaging (CfN).

Characteristics of the Study Population

Target population
Patients will be diagnosed with current Major Depressive Disorder as determined by meeting the DSM criteria for MDD; a subset of patients will be diagnosed with current Persistent Depressive Disorder (PDD) instead of current MDD, as per the May 2018 protocol. They will be otherwise healthy, right-handed, adults aged 18-60 years.

Subjects enrolled by Penn Researchers
95

Subjects enrolled by Collaborating Researchers
0

Accrual
All recruitment will be conducted through the University of Pennsylvania and surrounding community to find 40 individuals with MDD to complete the study with usable data. It is assumed that there will be approximately 55 participants who screen fail, are lost to follow up, withdraw, or complete without usable data. Therefore, we estimate that we will need to consent/enroll up to 95 participants overall, in order to adequately test the hypotheses.

Key inclusion criteria
1. 18-60, male or female, inclusive 2. Meets DSM-5 criteria for major depressive disorder (MDD) 3. Capacity to give informed consent and follow study procedures 4. Sufficient command of English language to understand and respond to written as well as verbal instructions 5. Right- handed

Key exclusion criteria
1. Significant disability (e.g., intellectual disability, blindness, deafness, etc.) 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 contraindications (e.g., seizure disorder, CNS active disorder, etc.) 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. Opiate medication, antihypertensive medication, or any medication that interferes with blood flow (interferes with fMRI recordings) 6. Current use of psychiatric medication, and unable/ unwilling to safely withdraw 2 weeks prior to study 7. Known neurological disorders (e.g., multiple sclerosis, encephalopathy, seizure disorder, brain tumors, etc.) 8. Diagnosis(es) of an exclusionary DSM-5 Diagnosis, including (but not limited to) bipolar disorder, schizophrenia, current severe substance use disorder, or any other diagnosis as determined by PI. 9. Refusal to abstain from illicit drug use for duration of the study 10. Refusal to abstain from alcohol within 24 hours of scans 11. Woman who is pregnant, breastfeeding, or trying to become pregnant (based on woman's attestation alone) 12. Any other factor that the investigator decides may affect patient safety or compliance (e.g., distance greater than 100 miles from procedure site)

Vulnerable Populations

	Children Form
	Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus) Form
	Fetuses and/or Neonates Form
	Prisoners Form
	Other
x	**None of the above populations are included in the research study**

The following documents are currently attached to this item:

There are no documents attached for this item.

Populations vulnerable to undue influence or coercion
None anticipated.

Subject recruitment
All participants will be recruited through the University of Pennsylvania and surrounding community. We will use IRB-approved flyers, brochures and online postings on Facebook, Twitter, Craigslist, iConnect, Penn newsletters and the CNDS website. Individuals will express interest by initiating contact with the research staff via phone or email for a phone-screening procedure or by completing an online screening form through Penn supported REDCap. The link for completion of online screening forms may be presented throughout all advertising mediums. All subjects meeting basic inclusion criteria will be scheduled for an in-person screening visit. 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). Additionally, subjects will be recruited through Penn's Office of Clinical Research iConnect volunteer registry. Volunteers who have consented to be contacted regarding studies of interest will be sorted by relevant diagnoses and invited by study team members to fill out an online survey to determine eligibility. An email script that will be used to contact volunteers has been attached.

Will the recruitment plan propose to use any Penn media services (communications, marketing, etc.) for outreach via social media avenues (examples include: Facebook, Twitter, blogging, texting, etc.) or does the study team plan to directly use social media to recruit for the research?
Yes

Please identify which method(s) of social media you will utilize, the content of the text to be used, and the method(s) for posting this information (i.e., using Penn supported communication services). When proposing the text to utilize, please be aware of any social media limitations (i.e., number of characters allowed in a tweet) and any appropriate confidentiality practices necessary to be compliant with posting research recruitment text.*
Our unit has a Facebook page, titled: "UPenn - Center for Neuromodulation in Depression and Stress" in which we will only post IRB-approved study advertisements for on-going studies in our program. We also plan to use Twitter to post IRB-approved study advertisements.

The following documents are currently attached to this item:

There are no documents attached for this item.

Subject compensation*
Will subjects be financially compensated for their participation?
Yes

The following documents are currently attached to this item:

There are no documents attached for this item.

If there is subject compensation, provide the schedule for compensation per study visit or session and total amount for entire participation, either as text or separate document

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. If subjects do not fully complete the study, they will receive compensation for the parts of the study they did complete, based on the following outline: Visit 1: Clinical Interview ($20.00) Visit 2: Baseline MRI Scan to determine TMS targets ($40.00) Visit 3: Baseline TMS/MRI Scan #1 ($60.00) Visit 4-6: TMS to the fMRI-guided site ($70.00 each, $210.00 total) Visit 7: Follow-up TMS/MRI Scan #2 ($120.00) Total compensation for full study completion is $510.00 for each subject. 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.

Study Procedures

Suicidal Ideation and Behavior
Does this research qualify as a clinical investigation that will utilize a test article (ie- drug or biological) which may carry a potential for central nervous system (CNS) effect(s)?
No

Procedures

Pre-screening: Participants may complete an online or phone screening form to see if they meet basic eligibility requirements. Screening will include the collection of contact information, basic demographics, and a brief medical and psychiatric history. Screenings will be recorded in REDCap; this data will be retained indefinitely. The screening data will not be used for analyses and will only be retained to help research staff monitor recruitment resources, reasons individuals do not meet eligibility, and to help avoid rescreening the same individuals. We request a waiver of HIPAA authorization for this aspect of the study. Visit 1/ Screening Visit: Informed consent will be obtained upon arrival for an initial visit and before any study-related procedures are conducted. The rest of this screening visit will include a structured diagnostic interview (SCID-5), psychiatric and medical evaluation, collection of demographic information, and a demonstration of TMS. 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 after. The information collected in this initial visit will determine if the subject meets all inclusion criteria. Upon meeting all criteria for inclusion in the study, subsequent dates will be set for the participant to complete all study-related procedures. Visit 2/ Initial MRI Scan: 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, using a Siemens 64-channel head coil. The total time in the scanner will be approximately 60 minutes. Based on our experience, this is well within patients ability to tolerate the scanning procedures without discomfort and without excessive motion. All MRI imaging protocols will be reviewed and approved by CAMRIS. An experienced technician and a member of the study team will be present during the MR session to ensure participant safety and well-being. If the participant complains of feeling claustrophobic and does not wish to complete the MRI, the study will be terminated. Emergency personnel and equipment are immediately available to the MRI room should the need arise. It is possible that during the course of the research study, the research staff may notice unexpected findings on an MRI scan. Should this occur, the findings will be assessed by a trained radiologist. The study doctor will inform research subjects of any significant findings. Visit 3/ TMS + MRI Baseline Scan: Participants will return for a subsequent MRI scan with concurrent TMS brain stimulations. The purpose of this TMS/MRI scan is to probe brain networks prior to the main stimulation protocols, which will occur at the subsequent visits. Brain data from the Initial 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. Our MRI-compatible TMS system (MagPro X100 Stimulator, MRI-B91 TMS coil) is housed in Stellar Chance at the 3-Tesla MRI machine. The apparatus was installed under the supervision of Mark Elliott, Ph.D. a member of CAMRIS, and we have attached a signed letter of support from Dr. Elliott for this protocol. Additionally, participants will complete a series of baseline clinical and neuropsychological assessments. Visit 4-6/ Mini TMS Sessions: Participants will return for 3 consecutive days (+/- 1 day). During each session, subjects will receive theta-burst stimulation (see Huang et al., 2005), which is a slight modification of the FDA-approved protocol for TMS. A normal, 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. We have attached several examples of prior studies which have safely utilized TMS outside of its FDA-approved protocol, even in heightened doses. Our study uses many fewer stimulations than these studies, and we are using the FDA-approved devices for treatment of depression in this protocol (MagPro X100 Stimulator, Cool-Coil B65 TMS coil). Please see the "Background" for more details. Patients will additionally complete a few brief assessments at these visits. Visit 7/ TMS + MRI Scan #2: This visit will mirror Visit 3, the baseline visit. There will be a 2-hour MRI/TMS scan and subjects will complete the same set of clinical and neuropsychological assessments from Visit 3.

The following documents are currently attached to this item:

There are no documents attached for this item.

Deception

Does your project use deception?
No

International Research
Are you conducting research outside of the United States?
No

Analysis Plan
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 round of stimulation influences symptoms.

The following documents are currently attached to this item:

There are no documents attached for this item.

Data confidentiality

- x **Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.**
- x **Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.**

  Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.
- x **Wherever feasible, identifiers will be removed from study-related information.**

  A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
- x **A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)**
- x **Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.**

  Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

Subject Confidentiality
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. Everything 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. Any documents connecting the code with the participant name will also be stored in secure cabinets inside locked rooms or in password protected, IRB compliant online databases, such as REDCap.

Sensitive Research Information*
Does this research involve collection of sensitive information about the subjects that should be excluded from the electronic medical record?
No

Subject Privacy
Privacy refers to the person's desire to control access of others to themselves. Privacy concerns people, whereas confidentiality concerns data. Describe the strategies to protect privacy giving consideration to the following: The degree to which privacy can be expected in the proposed research and the safeguards that will be put into place to respect those boundaries. The methods used to identify and contact potential participants. The settings in which an individual will be interacting with an investigator. The privacy guidelines developed by relevant professions, professional associations and scholarly disciplines (e.g., psychiatry, genetic counseling, oral history, anthropology, psychology).
Participants will be recruited through the University of Pennsylvania and surrounding community. For future contact, they will be asked if they prefer phone (cell or home) and/or email. The study will be presented in a private room and the fMRI will also take place in a private room. All contact made with the participant will be done so when the coordinator(s) or investigator are in private, as would be the

case with a doctor making a call to their patient. Participants will further be informed & required to provide verbal consent to have their phone screening information (written consent within online self-report screener) retained in REDCap.

Data Disclosure
Will the data be disclosed to anyone who is not listed under Personnel?
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.

*Data Protection**

- x **Name**
- x **Street address, city, county, precinct, zip code, and equivalent geocodes**
- x **All elements of dates (except year) for dates directly related to an individual and all ages over 89**
- x **Telephone and fax number**
- x **Electronic mail addresses**
- x **Social security numbers**
- x **Medical record numbers**
- x **Health plan ID numbers**
- **Account numbers**
- **Certificate/license numbers**
- **Vehicle identifiers and serial numbers, including license plate numbers**
- **Device identifiers/serial numbers**
- **Web addresses (URLs)**
- **Internet IP addresses**
- **Biometric identifiers, incl. finger and voice prints**
- **Full face photographic images and any comparable images**
- **Any other unique identifying number, characteristic, or code**
- **None**

Does your research request both a waiver of HIPAA authorization for collection of patient information and involve providing Protected Health Information ("PHI") that is classified as a "limited data set" (city/town/state/zip code, dates except year, ages less than 90 or aggregate report for over 90) to a recipient outside of the University of Pennsylvania covered entity?
No

Tissue Specimens Obtained as Part of Research*
Are Tissue Specimens being obtained for research?
No

Tissue Specimens - Collected during regular care*
Will tissue specimens be collected during regulator clinical care (for treatment or diagnosis)?
No

Tissue Specimens - otherwise discarded*
Would specimens otherwise be discarded?
No

Tissue Specimens - publicly available*
Will tissue specimens be publicly available?
No

Tissue Specimens - Collected as part of research protocol*
Will tissue specimens be collected as part of the research protocol?
No

Tissue Specimens - Banking of blood, tissue etc. for future use*
Does research involve banking of blood, tissue, etc. for future use?
No

Genetic testing
If genetic testing is involved, describe the nature of the tests, including if the testing is predicative or exploratory in nature. If predictive, please describe plan for disclosing results to subjects and provision of genetic counseling. Describe how subject confidentiality will be protected Note: If no genetic testing is to be obtained, write: "Not applicable."
Not applicable.

Consent

1. Consent Process

Overview
Consent will be obtained by research coordinators or the investigators. Consent will be obtained in a private room where the coordinator and investigator(s) can explain the purpose of the procedures and what they will add to our knowledge of MDD. They will explain that participating is completely voluntary and that not participating will not change access to treatment in any way. The potential participant will be given the option to consider study enrollment and will not be forced to make a decision the same day. If they decide to participate, a combined consent and HIPAA form will be signed by research staff and the patient. Participants will be given a copy of the consent form. The patient will be reminded before and after enrolling, and before any research procedure, that their participation is optional and has no impact on the care they can expect.

Children and Adolescents
N/A

Adult Subjects Not Competent to Give Consent
N/A - we are looking for cognitively normal participants, so all will have the competency to give consent.

2. Waiver of Consent

Waiver or Alteration of Informed Consent*
Waiver of written documentation of informed consent: the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context

Minimal Risk*

Impact on Subject Rights and Welfare*

Waiver Essential to Research*

Additional Information to Subjects

Written Statement of Research*
Yes

If no written statement will be provided, please provide justificiation

Participants will received a copy of their informed consent/HIPAA authorization forms; there will be no

written statement regarding the participants' screening information collected prior to consent; screening information will not be analyzed for any purposes.

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit

Potential Study 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 every 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. Our medical screening forms will serve as confirmation that a woman of child-bearing potential can participate in this study. An MRI scan requires subjects to be in a partially enclosed space inside the scanner. Some people may find this 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. An 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 and will be 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 entering 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. The specific form of TMS used in this study is called Theta Burst Stimulation (TBS). While this newer stimulation protocol is used widely, there is less research using TBS compared with other TMS procedures. TBS is not approved by the FDA for treatment of depression. There may be long-term risks due to TBS that are currently unknown. 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.

Potential Study Benefits
This study will provide no direct benefit to individual participants. However, the knowledge gained may hopefully help guide future treatments in depression and may help advance the field of psychiatry as a whole.

Alternatives to Participation (optional)
The alternative to participation is to not participate.

Data and Safety Monitoring
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. Detailed Data Safety Monitoring Plan: This section describes the Data and Safety Monitoring Plan and quality assurance (QA) procedures that will be used for this proposed study. This monitoring plan details the frequency of monitoring visits, regulatory document review, and compliance review. 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 deidentified 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.

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit Assessment
This study is minimal risk. There is essentially zero risk of harm from the research procedures (MRI, TMS, assessments of symptoms). The potential benefit to society through the increased understanding of treatment methods in MDD/PTSD far outweighs 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.

General Attachments

The following documents are currently attached to this item:

Cover Letter (2020.12.09_coverletter_825761.doc)

Informed consent form (2020.12.09_icf.v10_clean_825761.docx)

Informed consent form (2020.12.09_icf.v10_tracked_825761.docx)

Additional forms (2020.12.09_irbcorr_reenrolledpt_825761.pdf)