# Accelerated Theta Burst in Treatment-Resistant Depression: A Dose Finding and Biomarker Study

# NCT03680781

# December 20, 2024

## 1. PURPOSE OF THE STUDY

### a. Brief Summary

Repetitive transcranial magnetic stimulation (rTMS) is an established technology as therapy for treatment-resistant depression. The approved method for stimulation is 10Hz stimulation for 40 min over the left dorsolateral prefrontal cortex (L-DLPFC). This methodology has been very successful in real world situations. The limitations of this approach include the duration of the stimulation (approximately 40 minutes per stimulation session). Recently, researchers have aggressively pursued modifying the stimulation parameters to reduce stimulation times with some preliminary success.This study intends to further modify the parameters to create a more rapid form of the stimulation and look at the change in neuroimaging biomarkers.**Objectives**

This study will allow the investigators to understand if protocols developed for 4-6weeks worth of stimulation can be compressed over up to five days.

### c. Rationale for Research in Humans

All transcranial magnetic stimulation treatment studies must be conducted in humans.

## 2. STUDY PROCEDURES

### a. Procedures

Participants & Enrolment:
We will recruit 90 participants aged 18-75yo for both phases of this trial receiving open label stimulation: intermittent theta burst (iTBS) over L DLPFC (up to five days 10x/day). The study will have 3 time periods and an additional 2 time periods for some participants:
- screening time period
- baseline time period
- acute study time period
- follow-up time period

We will utilize a modified study design version of Li et al (Li et al., 2014) and Duprat et al (Duprat 2016).

**Due to COVID-19, we may conduct screening and study visits via Zoom whenever in-person contact needs to be limited. See below for details.

We have also attached a COVID-19 screener that we may use to screen participants for symptoms of COVID-19 any time prior to in-person visits**

Screening Time-Period:
Patients will undergo a screening phase, which may occur any time prior to the active study period, where their eligibility will be confirmed. Providers will perform: informed consent, screen for inclusion and exclusion criteria, MRI safety, Tass, medical and psychiatric history, physical exam, vital signs, urine tox screen, pregnancy test, saliva cortisol. Diagnosis will be confirmed with the MINI or SCID (if performed previously for another study). Patients will be staged using the Maudsley staging method and a trained rater will perform baseline C-SSRS, HAMD-21, MADRS, CGI-S, YMRS, SSI, Thase-Rush, and SHAPS. PIRS-20, BDI-2, DKEF. Trials may be included. HDRS

Baseline:
Baseline visits may be separate from screening visits due to time constraints. In this case, baseline measures identical to those in the screening time-period may be performed again.

Acute Study Time-Period: Participants will receive 10 daily stimulations with active iTBS over the left dorsolateral prefrontal cortex (LDLPFC)(1800 pulses) or bilateral iTBS (L-DLPFC, 1800 pulses) and right dorsolateral prefrontal cortex (RDLPFC) (600 to 1800 pulses). The L-DLPFC and RDLPFC targets will be targeted utilizing the Localite or Soterix Neural Navigator (Netherlands) neuronavigation system. Use of Scripts: For the targeting (pre-iTBS) scan, as we have done in prior studies, a clustering algorithm will be applied to each participant's resting state scan to identify personalized functional subregions within both the L-DLPFC or R-DLPFC and sgACC. The extent of anti-correlation of each of the L-DLPFC or R-DLPFC functional subregion with the sgACC as well as its size and shape (based on spatial concentration) will be considered to determine which will be used as the stimulation target.
The L DLPFC treatment target will be located via the Neural Navigator neuronavigation System (Soterix, New York, USA) by the psychiatrist as has been approved by the FDA. Custom MATLAB scripts will be used to further specify a point within the left or R DLPFC that is maximally anticorrelated with the sgACC, which will serve as the target for stimulation. Current literature supports this target within the DLPFC target as the most promising candidate for depression treatment (Weigand et al., Biol Psych, 2018 and Cash et al., Biol Psych, 2019).

We will ask each participant prior to the start of each treatment session, whether they have consumed any alcohol within the last 24 hours. If a participant appears intoxicated, we will use a validated scale that is frequently utilized in emergency rooms to screen for intoxication. We will use the Hack's Impairment Index (HII), uploaded in section 16. If participants are intoxicated, they will not be able to participate in the treatment sessions until they are sober. Each session will be separated by a 30 to 45-minute break. This separation between stimulation sessions decreases the risk of associated TMS side effects(e.g. irritation from the device, headache).

Prior to the start of each session, patients may be given the HAM-6 and pre-session brief assessment. Prior to starting each session we will administer an inter-session check in to monitor any symptom changes. Sessions will be scheduled in a 5-day sequence, resulting in a total of up to 50 sessions over up to 5 days. Each session is separated by a 35-45 min break. This separation between stimulations decreases the risk of associated TMS side effects (e.g. irritation from the

device, headache). During breaks, patients may participate in iPad or audio based cognitive behavioral therapy activities or mindfulness content. They may be asked to rate how much they enjoy this content on a scale from 1- 10.

During the acute study phase, patients may receive the following assessments each day following stimulation: MADRS-S and YMRS, as well as self-reported medication reviews. PIRS-20 and HAM-6 may be included. A post stimulation MRI will be performed following completion of the acute study phase (further details below).

Follow-up Time-Period:
Patients will have follow-ups at immediate-post stimulation and at weeks 1 ,2, 3, 4, 6, and 8 after the final TBS stimulation. A trained rater will perform HAMD-21, MADRS, SHAPS, SSI and YMRS at the mandatory in-person visits of immediate post and 4-week post stimulation. The other follow-up appointments will be shorter and consist of MADRS-S self-report. SHAPS, HAMD6, SSI and YMRS assessments may be conducted. The mandatory in-person visits are the immediate post and 4-week follow-ups, all other follow-ups may be conducted via ZOOM video call or phone. ESS may be included. Following this period, HAM-6 will be performed every two weeks (by phone or video call) for 6 months for all remitters and responders (defined by a 50% decrease in baseline MADRS score) . Additionally, DKEF and may be performed after stimulation and at 4 weeks post stimulation. All participants will be offered additional aTBS weeks if they elect and if the investigator deems necessary. If participants return to baseline levels of depression or are deemed as "non-responders" (defined by a less than 50% decrease in baseline MADRS and/or HAMD21 scores) within the 6-month follow-up period, they will be referred to outpatient TMS care and be disenrolled from the study.
---

Cognitive Measures:
Color/Word interference (from D-KEFS or Stroop), Trail Making Test (DKEFS or TMT A & B), and Digit Span (from WAIS-IV): All may be assessed prior to stimulation, immediately after 5 days, and one month after stimulation.

EEG:
EEG measurements may be collected to provide supplemental data.

Heart Rate:
We may collect pulse and heart rate variability measurements at all or some of the established time points for the active study in order to assess how aTBS stimulation effects heart rate.

Imaging and Biomarkers:
We will perform resting state functional connectivity MRI prior to acute study phase, immediately after acute study phase (1-3 days following final aTBS stimulation), and at one-month post-stimulation (between 25-30 days following the final aTBS stimulation). At the acute phase, we will acquire a structural scan. Scans for functional MRI will be undertaken at a study visit at the CNI on the Stanford campus.

Following informed consent, clinical interviews and behavioral testing will occur at a study visit at the Stanford Psychiatry department. During scans, the Suicide Stroop will be performed to

assess suicidality. Sadness induction will be tested using validated IAPS pictures (International Affective Picture System (IAPS): Instruction Manual and Affective Ratings (1999): International Affective Picture System (IAPS): Instruction Manual and Affective Ratings.) Clinical interviews, behavioral studies and imaging details for this phase are outlined below.

---

Data Collection:

The primary outcome measure for this study will be change in HAMD-21 score. The HAMD-21 is a clinical assessment tool used to rate a patient's level of depression and is the standard scale used for depression research studies. Secondary measures will include functional connectivity change of the subcallosal cingulate to the default mode network and within the default mode network. Primary outcome will be assessed as the change between baseline and 4 weeks post-stimulation, with secondary measures to include the change between baseline and immediately post-stimulation. Other secondary measures include heart rate/heart rate variability, and clinical interview assessments, to be performed according to the timeline above, include:

MINI-Plus standardized interview for criteria for mood and anxiety disorder: To be assessed at screening to confirm MDD diagnosis.

HAMD-21 (Hamilton Depression Rating Scale 21-Item)

MADRS (Montgomery Asberg Depression Rating Scale)

C-SSRS (Columbia Suicide Severity Rating Scale)

HAM-6 (Hamilton Depression Rating Scale 6-Item)

C-SSRS (COLUMBIA-SUICIDE SEVERITY RATING SCALE)

CGI-S (Clinical Global Impressions Scale)

BDI-2 (Beck Depression Inventory II)

QIDS (Quick Inventory of Depressive Symptomatology)

YMRS (Young Mania Rating Scale)

DKEF Trials (Delis-Kaplan Executive Function System)

Quality of Life, Enjoyment and Satisfaction Questionnaire (40) - QLES-Q-SF

Medical Outcomes Study Short Form-36 - MOS-CORE-36

PIRS-20: Pittsburg insomnia rating scale

Acquisition and data extraction:

Clinical interview ratings will be made by trained study personnel.

Each self-report questionnaire will be acquired with computerized delivery. Individual item scores will be recorded and then summed according to symptom cluster and scale definitions.

Functional Neuroimaging:

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

Details regarding neuroimaging:

The subjects will undergo an MRI scan of the brain that will require about 1 hour in the MRI scanner. A structural MRI scan, fMRI scan will be done using a 3T system at Stanford facilities. During the scan, subjects will lie on the table in the magnet for 1 hour while the images are acquired. Instructions may be given through an auditory system. Subjects will wear earplugs and may be fitted for a bite bar to help them to keep their head still during the scans; for studies that enroll older adults, a bite bar will not be used so as to accommodate participants with dentures. These procedures have been used previously in younger and older adults alike, and do not cause undue distress in subjects. Brain images will be made using conventional MRI imaging (including functional and diffusion tensor imaging). Patients will undergo a minimum of 3 scans, each 1 hour in length, up to a maximum of 6 scans, each 1 hour in length. The standard of care regarding incidental findings that will be communicated to patient is as follows: The investigators for this project are not trained to perform radiological diagnosis, and the scans performed in this study are not optimized to find abnormalities. The investigators and Stanford are not responsible for failure to find existing abnormalities in your MRI scans. However, on occasion the investigator may notice a finding on an MRI scan that seems abnormal. When this occurs, a radiologist will be consulted as to whether the finding merits further investigation, in which case the principal investigator of the research study being conducted will contact the participant's primary care physician and inform them of the finding. The decision as to whether to proceed with further examination or stimulation lies solely with the participant and his/her physician. The investigators, the consulting radiologist, and Stanford are not responsible for any examination or stimulation that you undertake based upon these findings. Because the images collected in this study do not comprise a proper clinical MRI series, these images will not be made available for diagnostic purposes. In the event that a potential abnormality on the MRI images is detected by the researchers, the magnet manager, is to be notified immediately to report the potential issue. Films of images will not be provided to the researcher or volunteer scan subject as the images were obtained using a research MRI scan protocol and not from a clinically ordered MRI scan protocol prescribed by a radiologist at Stanford.

We will share data with IRB-37224 if the participant is consented for
both studies.

Video/audio recording the study consent and assessments:
We will video/audio record the study consent and clinical assessments conducted with participants while enrolled in the study. The video/audio recordings will be recorded using Zoom video from an encrypted Stanford owned laptop. The recordings will be available for training purposes for study personnel only. We will not use or distribute the video/audio recordings to outside personnel or scientific meetings etc. unless directly indicated by the participant on the video/audio consent section in the screening consent form.
**********
*
COVID-19 PRECAUTIONS
We will conduct all in-person clinical and self-report assessments at all study time points (screening, baseline, daily, and follow-ups )over Zoom video and/or REDCAP in cases where COVID-19 prevents in-person participation. These assessments will be audio and video recorded as described below.
We have added a COVID-19 screening questionnaire that we will implement at screening and at all in-person visits (ex. treatment days, MRIs, etc.).

**b. Procedure Risks**

These methods are the least risky because the intervals of stimulation have been shown to be appropriate for theta burst stimulation in the motor system with no adverse outcomes.**Use of Deception in the Study**

No deception will be used.

**d. Use of Audio and Video Recordings**

Video and Audio Recordings:

We will be video and audio recording study participants during the clinical assessments conducted with them while enrolled in the study. The video and audio recordings will be recorded using Zoom video from an encrypted Stanford owned laptop. The recordings will be available for training purposes for study personnel only or as otherwise consented to on the consent form. We will not use or distribute the recordings to outside personnel or scientific meetings etc. unless directly indicated by the participant on the consent form.

**e. Alternative Procedures or Courses of Treatment**

**f.** Participants with insurance could alternatively receive traditional rTMS. **Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?**

The participants will have the option of pursuing treatment as usual after the study (medications, therapy, traditional rTMS).

**g. Study Endpoint(s)**

The study will end after 6 months.**BACKGROUND**

**a. Past Experimental and/or Clinical Findings**

There is early indication that utilizing theta burst stimulation (TBS), which mimics natural brain rhythms, is an effective stimulation method for modulation of human cortex(Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). While first utilized in the motor cortex, TBS has been since utilized in the limbic and cognitive areas with some early success in treating depression(Chung, Hoy, & Fitzgerald, 2015). The benefits of this form of stimulation is that it appears to allow for a reduction in the time of stimulation while maintaining a similar efficacy to traditional 40 min 10Hz rTMS stimulation in an early comparison study(Bakker et al., 2015). It is clear that the dorsolateral prefrontal cortex and specifically the posterior middle frontal gyrus is heavily implicated in the pathophysiology of at least some depression endophenotypes. In depression, the left DLPFC hypoactivity is associated with negative emotional judgment and right DLPFC hyperactivity is linked to attentional modulation(Grimm et al., 2008). Additionally, the DLPFC is a component of the cognitive control network (CCN), and the modulation of this node appears to modulate the CCN. At least four groups have performed TBS to the DLPFC where the left DLPFC received iTBS (excitatory) and the right received cTBS (inhibitory)(Chung et al., 2015).

There is emerging evidence from the motor system that the spacing (or timing) between theta burst trains is important in the LTP/LTD. If the train goes on for two long without a necessary time interval, there is a reversal of the initial direction (LTP or LTD)(Gamboa, Antal, Moliadze, & Paulus, 2010). There has been a progression in the literature that if there is approximately an hour of spacing in between the theta burst trains, there is an EEG resolution and an apparent additive effect of the stimulation towards the desired direction (LTP or LTD). There is at least 30 minutes of neurophysiological changes on qEEG after theta burst stimulation(Noh, Fuggetta, Manganotti, & Fiaschi, 2012). In a visual neglect TBS study, there was a non-linear increase in the duration of stimulation effect with the doubling of pulse trains(Nyffeler, Cazzoli, Hess, & Muri, 2009). It appears that it is best to separate the pulse trains by one hour (Cazzoli et al., 2012).

## 4. DEVICES USED IN THE STUDY

### a. Investigational Devices (Including Commercial Devices Used Off-Label)

| **Investigational Device 1** | |
|---|---|
| Name: | MagPro X100 |
| Description: | Transcranial Magnetic Stimulation Device with theta burst stimulation |
| Significant Risk? (Y/N) | No |
| Rationale for Non-Significant Risk | The 'traditional 10Hz TMS' is on label and the theta burst stimulation is off label. It is the same device for both. The Magventure is about to be approved by the FDA for depression in 2 weeks. When that happens, the 'traditional 10Hz' stimulation will be on label with an approved device. The theta burst stimulation is minimal risk because the risk of seizure is very low (only reported once in literature) and there is no other risk other than minimal scalp irritation. We will be using an approved device 'off label' stimulation parameters which has a lower risk profile than the on label approved parameters. |
| **Investigational Device 2** | |
| Name: | NextStim |
| Description: | N/A |
| Significant Risk? (Y/N) | No |
| Rationale for Non-Significant Risk | FDA approved device for treatment of depression We will be using the NextStim TMS device in an "off label" treatment paradigm. The FDA has reviewed our proposed treatment paradigm parameters for our inpatient studies epro #41071 and #47771 and has deemed our parameters as a non-significant risk. I have attached the FDA letter to section 16. Moreover, this device was approved for use in our outpatient blinded study epro #33797 which also uses the same paradigm, in treatment-resistant depressed patients. We will be using the exact same parameters as the above studies (10 sessions of ~9min accelerated theta-burst stimulation every day for 5 days with 50 min inter-sessional intervals) in this study. The participants we recruit for this study are also treatment resistant depressed patients. We screen out anyone who may have increased risk of seizure, which is the main risk of any TMS protocol, to prevent any change in risk. This is the rational why the device is an NSR for these participants. |
| **Investigational Device 3** | |
| Name: | 3T UHP |
| Description: | It is a non-invasive imaging scanner. Some of the radio frequency imaging coils, imaging software and devices being used in the scan are not approved by the FDA but are similar to counterparts that have been approved by the FDA. There are currently no known harmful side-effects associated with temporary exposure to the strong magnetic field used by MRI scanners. There is a small risk of heating from the cables associated |

| | |
|---|---|
| | with these devices. However, they do not pose a serious risk to the health, safety, or welfare of a subject. |
| Significant Risk? (Y/N) | No |
| Rationale for Non-Significant Risk | The 3T Ultra-High Performance (UHP) MRI scanner from GE is an upgrade to the 3T MR750 which was a commercial FDA-approved system. The UHP system utilizes many components from GE's 3T Signa Premier, including gradient drivers, power supply, transmit and receive system electronics, but uses a higher performance gradient coil. The 3T UHP system is not FDA approved and is subject to the 21 CFR 812 investigational device(IDE) regulations as well as 21 CFR 50 and 56. The system has been tested by GE according to UL606001-1 and also for compliance with IEC 60601-2-33 (ed 3.1) -- meeting limits and guidelines for peripheral nerve stimulation, patient thermal, SAR limit, acoustic noise, flammability rating UL94-5VA for safety covers, hydrostatic pressure, electrical hazards, dielectric strength and pinch point. The MRI scans in this study will also utilize operational parameters within FDA guidelines for Nonsignificant Risk thus an Investigational Device Exemption (IDE) from FDA should not be necessary. In addition, the MR research being conducted requires highly specialized software that does not exist in the clinical MR market, so it is designed and implemented by researchers at the CNI. Any such software will be considered investigational, will function as a non-significant risk device, and is subject to the 21 CFR 812 investigational device (IDE) regulations as well as 21 CFR 50 and 56. The investigational image acquisition software will conform to FDA guidelines for MR safety related to heating (SAR), peripheral nerve stimulation (dB/dt), and acoustic noise. |
| **Investigational Device 4** | |
| Name | MagPro XP |
| Description | Transcranial Magnetic Stimulation Device with theta burst stimulation |
| Significant Risk? (Y/N) | No |
| Rationale for Non-Significant Risk | Traditional 10 Hz TMS is on label and theta burst stimulation is off label. It is the same device for both. The MagVenture is about to be approved by the FDA for depression. When that happens, the traditional 10 Hz stimulation will be on label with an approved device. Theta burst stimulation is minimal risk because the risk of seizure is very low (only reported once in literature) and there is no other risk other than minimal scalp irritation. We will be using an approved device 'off label' stimulation parameters which has a lower risk profile than the on label approved parameters. |
| **Investigational Device 5** | |
| Name | Neural Navigator (Soterix) |
| Description | The study psychiatrist will use the Neural navigator neuronavigation system (Soterix)to identify our L DLPFC treatment target in conjunction with the FDA approved method. |
| Significant Risk? (Y/N) | No |
| Rationale for Non-Significant Risk | Soterix is an FDA approved neuronavigation device. Its FDA cleared indicated use is for TMS targeting using the CloudTMS system. We will use Soterix as a neuronavigational system for our TMS targeting using the Magventure TMS system specific coil (instead of CloudTMS system). Soterix qualifies as a NSR device because we are using it for the FDA-approved methodology of TMS targeting and it does NOT present a potential for serious risk to the health, safety, or welfare of a subject. |
| **Investigational Device 6** | |
| Name | Scripts |
| Description | Scripts used in conjunction with FDA approved Neural Navigator to supplement conventional FDA approved TMS targeting (within the L DLPFC). |
| Significant Risk? (Y/N) | No |
| Rationale for Non-Significant Risk | Our scripts are a NSR because we will be using them in conjunction with the FDA approved neuronavigation device to target the L DLPFC. Current clinical TMS targeting methods involve using a paper ruler and the 5cm |

| | |
|---|---|
| | rule (George et al, 1995), which has been reported to miss the L DLPFC target ~33% of the time (George et al, 2010). Our L DLPFC treatment target will ultimately be determined by the study psychiatrist, as FDA approved, and supplemented by our scripts in conjunction with the Soterix neural navigator. Thus, we will de-risk participants by targeting the L DLPFC 100% of the time. |

## 5. PARTICIPANT POPULATION

**a. Planned Enrollment**

**b.** We will recruit 90 participants only at Stanford, of no specific type.

**c. Age, Gender, and Ethnic Background**

We will recruit 90 participants aged 18-75, all gender and ethnic background.

**d. Vulnerable Populations**

We will not include children, pregnant women, decisionally impaired. We will include economically/educationally disadvantaged as well as homeless because this may be a way for them to receive rTMS treatment. We will include employees and students because while rTMS is approved by the FDA, it is not covered by many insurance carriers, and this would be a way for them to receive treatment. rTMS is a low-risk procedure, but we will ensure all safety measures are taken for these participants. We will not include any patients with shrapnel or any ferromagnetic within the head.).

**e. Rationale for Exclusion of Certain Populations**

Women and minorities are included. Children are not included because they are typically excluded from psychiatric interventions e.g., aTBS and children will not be clinical staff numbers.

**f. Stanford Populations**

N/A

**g. Healthy Volunteers**

N/A

**h. Recruitment Details**

Patients will be recruited through the outpatient clinic in the psychiatry department, through a database of potential research subjects that have consented to contact for future research through the depression research clinic and through physician referral. Patients will either directly contact the research team for study participation, or they will give consent to the referring physician and the physician will communicate directly with the study team.

We have a bipolar pre-screening REDCAP database which we will use to screen eligibility.

We will also use the Stanford Research Registry (protocol 25422) to recruit study participants. The research registry is a list of individuals who have consented to be contacted by researchers at Stanford and at present includes over 1,000 volunteers.

For participants who participate in studies IRB 33797 and IRB 37224, data will be shared with studies IRB 33797 and IRB 37224.

Flyers will be used to recruit as well.

**i. Eligibility Criteria**

i. Inclusion Criteria

90 participants aged 18yo-75yo with a primary diagnosis of major depressive disorder in a current major depressive episode or bipolar affective disorder in a current major depressive episode. Participants must qualify as "Moderate or Severe Treatment Refractory" using the Maudsley staging method, which incorporates past treatments, severity of symptoms and duration of presenting episode. Participants may continue antidepressant regimen but must be stable for 6 weeks prior to enrollment in the study. They must maintain that same antidepressant regimen throughout the study duration. All participants are required to have a stable psychiatrist for the duration of study enrollment

ii. Exclusion Criteria

1. All portions of study: History of MI, CABG, CHF, or other cardiac history.
2. - Any neurological condition
3. - History of epilepsy
4. - OCD
5. - Independent sleep disorder
6. - Autism Spectrum Disorder

**j. Screening Procedures**

Participants will be seen in the depression research clinic for depression treatment consultation. At that time, standard of care treatments will be offered as well as this protocol. To reduce the risk of the COVID19 virus, when a remote screening is conducted, electronic signature of consent will be obtained via Adobe sign. eConsenting via part 11 compliant Adobe Sign. Patients will receive an email with the following text:

Hello, Thank you for your interest in our study. Attached please find the informed consent form (ICF) discussed with you today. Please follow the Adobe Sign instructions to fill out and sign the ICF. If you have any questions, please call, or email the study team at 650-800-6920 or sainttmsstudy@stanford.edu.

**k. Participation in Multiple Protocols**

We will not enroll participants that are involved in any other treatment trial. We will coordinate with any ongoing biomarker studies to ensure that the treatment follows the biomarker study.

**l. Payments to Participants**

There will be no payment.

**m. Costs to Participants**

No cost to the participant.

**n. Planned Duration of the Study**

i. 1 day
ii. Maximum of 10 days of active study participation (active study period includes pre-measurements, 5 stimulation days, and post-measurements). 4 weeks follow-ups (1 appointment per week), after which up follow-ups will continue bi-weekly for up to 6 months. All follow ups during this time will be offered via video conferencing or telephone call (1 appointment every 2 weeks/twice per month).
iii. 6 months.

## 6. RISKS

**a. Potential Risks**

Repetitive transcranial magnetic stimulation is generally regarded as safe and without any serious or lasting adverse effects (Wasserman 1998; Rossi 2009). Inadvertent induction of a seizure is the most medically significant potential safety concern. However, there is no known risk of seizure for the above-stated brain stimulation parameters. The motor threshold is reflective of stimulation output necessary to cause neuronal depolarization. Since its first use in 2005, only one case of TBS has resulted in seizure, which occurred for stimulation at >100% resting MT (120% of aMT) and this was continuous TBS not iTBS. This proposed protocol involves iTBS delivered at 90% motor threshold. Finally, the proposed stimulation parameters mirror those used in Stanford IRB-approved TBS protocols (Protocol Director; ID 33797, ID 38138), which have received a ?minimal risk? designation. FDA approved rTMS has a 1:30,000 chance of seizure. According to a review published in the International Journal of Neuropsychopharmacology, there have been 4 cases of treatment-emergent mania induced using rTMS (3 bipolar patients, 1 MDD patient) (Xia et al. 2008) Currently, no known cases of either risk (seizure or mania) has been reported in iTBS according to a review in The Journal of Nervous and Mental Disease (Rachid 2017)

Additionally, the following expected AEs were reported in association with TMS in a recent publication (Downar et al, 2018): Headache, nausea, dizziness, fatigue, insomnia, anxiety, or agitation, back or neck pain, vomiting, tinnitus, migraine aura, abnormal sensations, unrelated accidents, and unrelated medical problems such as cold and flu. Citation: Downar et al (2018). Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a

randomized non-inferiority trial. The Lancet. We do not anticipate any foreseeable risks of using the scripts in this study. All targets will be cross checked and validated with a study physician using the FDA approved clinical paradigm. The clinical method for TMS targeting of the L DLPFC uses a paper ruler and the 5cm rule (as described by George et al, 1995; George et al, 2010). The treatment target (L DLPFC or R DLPFC) will be located via the Neural Navigator neuronavigation System (Soterix, New York, USA) by the psychiatrist as has been approved by the FDA. Custom MATLAB scripts will be used as a supplement to further specify a point within the L DLPFC that is maximally anticorrelated with the sgACC, which will serve as the target stimulation. Current literature supports this target within the L DLPFC target as the most promising candidate for depression treatment (Weigand et al., Biol Psych, 2018 and Cash et al., Biol Psych, 2019). We will be decreasing risk by using our scripts.

i. Investigational drugs

N/A

ii. Commercially available drugs, biologics, reagents, or chemicals

N/A

iii. Procedures

The risks of the rTMS procedure being performed are Mania/hypomania and Seizure.
The potential risks for MRI procedures are:

- Exposure to magnetic field of MRI which may possibly lead to a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and should not be painful.
- Dizziness or nausea may occur if you move your head rapidly within the magnet.
- The scanner uses a very strong magnet that will attract some metals and affect some electronic devices. These devices include cardiac pacemakers, surgical clips and implants that are in or on your body.
- Some of the radio frequency imaging coils, the imaging software and other devices being used to perform scans are not approved by the FDA, thus are considered experimental in nature.
- Some of the images, words, and sounds presented while you are in the scanner will have an emotional content and so could be mildly upsetting to some individuals.

iv. Radioisotopes/radiation-producing machines

N/A

v. Physical well-being

Participants will have all measures exerted to reduce the chances of seizure and discomfort from stimulation

vi. Psychological well-being

Participants will be placed in a relaxing environment to promote psychological well-being.

vii. Economic well-being

Participant's economic well-being will be looked at for as the participant will be receiving an intervention that would normally cost $10,000 and not paid for by most insurers.

viii. Social well-being

We would anticipate that particularly the responders that perceived social wellbeing would improve. We do not anticipate that there would be any worsening

ix. Overall evaluation of risk

Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

---

**b. International Research Risk Procedures**

N/A

---

**c. Procedures to Minimize Risk**

We will have a trained rTMS treater monitoring for changes in level of consciousness at all times. We will eliminate any offending agents that may increase risk of seizure. Monitoring participants depressive symptoms will allow the identification of individuals at risk of suicide and therefore the risk of this occurring can be minimized. The patient's psychiatrist will be immediately notified if participants show signs of suicidal ideation, hypomania/mania (increase of 4 or more items by at least 1 point on the YMRS scale) or display depressive symptoms which are worse than baseline (by 5 points on the HAMD compared to the HAMD score the patient had before study enrollment. If any study personnel believe a participant is at risk, the PI Dr. Nolan Williams (psychiatrist) will be notified immediately and an emergency consultation between him and the participant will be had. If the PI considers it necessary, the patient will be referred for emergency psychiatric treatment.

If the participant displays an increased YMRS score (>/=2 points) on 2 questions, stimulation will be switched to all right sided treatment to prevent any possibility of further inducing hypomania or mania. If these symptoms persist or increase to any greater degree during that same treatment series, the patient will be treated with Ativan and their primary psychiatrist will be contacted by the PI. If any of the research team or clinical staff believe that the participant may be showing signs of hypomania/mania, the YMRS will be administered by trained personnel immediately, the researchers will not wait until the daily assessments are conducted.

---

**d. Study Conclusion**

The experiment will terminate when the final participant has completed their treatment and all data has been analyzed.

**e. Data Safety Monitoring Plan (DSMC)**

i. Data and/or events subject to review

Adverse events, protocol deviations, aggregate data will all be frequently reviewed by the Study PI and Protocol Director (PD).

ii. Person(s) responsible for Data and Safety Monitoring

The Principal Investigator and Protocol Director

iii. Frequency of DSMB meetings

N/A

iv. Specific triggers or stopping rules

If there is evidence of significant risk to the participants such as multiple seizure events or worsening of psychiatric state in a large majority of the participants.

v. DSMB Reporting

N/A

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

Yes

vii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

No

**f. Risks to Special Populations**

N/A

## 7. BENEFITS

Participants have a good chance of improvement in their mood symptoms as versions of this new type of rTMS treatment has already demonstrated consistent efficacy.

## 8. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.