Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression (SAINT-TRD)

NCT03068715

September 18 2018

Nolan Williams, Principal Investigator
Stanford University
Stanford, California 94305

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 treatment is 10Hz stimulation for 40 minutes over the left dorsolateral prefrontal cortex (L-DLPFC). This methodology has been very successful in real world situations. The limitation of this approach includes the duration of the treatment (approximately 40 minutes per treatment session). Recently, researchers have aggressively pursued modifying the treatment parameters to reduce treatment times with some preliminary success. This study intends to further modify the parameters to create a more rapid form of the treatment and look at the change in neuroimaging biomarkers.

b. Objectives

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

The primary outcome measure for this study will be change in MADRS score. The MADRS is a clinical assessment tool used to rate a patient's level of depression and is the standard scale used for depression research studies.

Secondary measures will include functional connectivity change of the subcallosal cingulate to the default mode network and within the default mode network.

c. Rationale for Research in Humans

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

2. STUDY PROCEDURES

a. Procedures

We will recruit a total of 60 participants for this trial:

-30 (aged 18-80yo) receiving: intermittent theta burst (iTBS) over L DLPFC (five days 10x/day)
-30 (aged 18-80yo) receiving identical sham stimulation over L DLPFC with sham iTBS (five days 10x/day)

For this study, we will be using the MagPro double blinded rTMS Research System and the randomization occurs within the system such that the control sounds like and utilizes the same stimulation parameters as the real TMS.

This allows for the stimulation to be blinded to the treater and the participant.

Participants will have moderately treatment resistant major depressive disorder as defined by a score of >/=20 on the HAMD-17, MADRS and BDI-II scales.

Screening Time-Period:

Patients will undergo a screening time period where their eligibility will be confirmed. This may occur any time prior to the baseline time period. Following screening informed consent, clinical interviews and behavioral testing will occur at the Stanford Psychiatry department. The clinical interview will include a screen for inclusion and exclusion criteria, MRI safety, TASS, medical and psychiatric history, neurological exam, urine tox screen, pregnancy test, and motor threshold (see Motor Threshold section for details below).

Diagnosis will be confirmed with the MINI and/or SCID. We will also request medical records to confirm information collected during the screening visit. Patients will be staged using the Maudsley staging method and a trained rater will perform: HAMD-21, MADRS, ATHF, YMRS and SSI.

Patients will fill out self-reports including the BDI-II and C- SSRS.

Baseline Time-Period:

Baseline visits will be separate from screening visits to confirm stability of symptoms (stability is defined as a difference in MADRS score below 30% from screening).

Participants will have an MRI scan in the morning.

Baseline clinical measures (MADRS and HAMD-17) will be performed. In addition, patients will fill out the C-SSRS self-report.

Participants will practice using the heart rate monitor that they will be using for the remainder of the study.

Active Study Time-Period:

iTBS sessions will be scheduled in a 5-day sequence, resulting in a total of 50 sessions over 5 days. Participants will receive 10 daily stimulations with active or sham iTBS (see double-blinded rTMS system for details below). Each session is separated by a 50-minute break. This separation between sessions decreases the risk of associated TMS side effects (e.g. irritation from the device, headache).

Follow-up Time-Period:

Patients will have the same clinical assessments as well as MRI scans that were completed during the baseline time-period at the immediate post-treatment and 1-month post-treatment mark. Heart rate will be measured during these time points.

Motor threshold:

Using single pulse TMS, the scalp position of lowest motor threshold for the right first dorsal interosseous or abductor pollicis brevis muscles will be determined.

Resting motor threshold (MT) was defined using the Adaptive Pest online algorithm.

Double blinded rTMS system:

For this study, we will be using the MagPro double blinded rTMS Research System and the randomization occurs within the system such that the control sounds like and utilizes the same stimulation parameters as the real TMS. This allows for the stimulation to be blinded to the treater and the participant. A third party not otherwise involved in the study will hold the blinding codes for the study. Blinding codes will be assigned randomly to each patient.

During treatment, the blinding code is entered into the MagPro device and the device determines which treatment (Active or sham) to apply. Following the first day of treatment, subjects will be asked if they believe they are receiving active or sham treatment. This information will be collected to determine the success of the blinding procedure.

Blinded Phase:

A Magventure double blind key will be inputted into the Magventure double blind system during the blinded study week.

Participants in the active stimulation group will receive intermittent TBS (intermittent TBS-1800 pulses/session). They will receive 1800 stimuli of iTBS to left DLPFC per session per session.

Participants in the sham stimulation group will receive sham intermittent TBS (intermittent TBS-1800 pulses/session). They will receive 1800 stimuli of sham iTBS to left DLPFC per session.

The L-DLPFC will be targeted utilizing the Localite neuronavigation system if using the Magventure device.

Stimulation intensity will be standardized at 90% of RMT and adjusted to the skull to cortical surface distance (see Nahas 2004). Sessions will be delivered using the MagPro stimulator, with 3-pulse 50-Hz bursts given every 200ms (at 5 Hz). In the intermittent TBS, a 2s train of bursts will be given every 10 s for a total of 570s (1800 pulses) over the L DLPFC.

Heart Rate Monitors:

We will collect heart rate and heart rate variability measurements at all or some of the established time points for the active study in order to assess how aiTBS stimulation affects heart rate. Some participants may have to shave areas of their chest in order for the heart rate monitor electrodes to stick in place.

Imaging and Biomarkers:

We will acquire MRI scan sequences prior to active study phase, immediately after active 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 structural scans and functional scans at the CNI on the Stanford campus.

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.

The subjects will undergo an MRI scan of the brain that will require about 1 hour in the MRI scanner. A structural MRI scan and an 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 up to a maximum of 6 scans, each 1 hour in length.

Acquisition and data extraction:

Clinical interview ratings will be made by trained study personnel. Individual item scores will be recorded and then summed according to symptom cluster and scale definitions.

Outcome measures:

The primary outcome measure for this study will be change in MADRS score. The MADRS is a clinical assessment tool used to rate a patient's level of depression and is the standard scale used for depression research studies.

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 immediate post-stimulation, with secondary measures to include the change between baseline and immediate post-stimulation and 1-month post-stimulation.

Other secondary measures include heart rate/heart rate variability and the clinical interview assessments, to be performed according to the timeline above, include:

HAMD-17 (Hamilton Depression Rating Scale 17-Item)
C-SSRS (Columbia Suicide Severity Rating Scale)
HAMD-6 (Hamilton Depression Rating Scale 6-Item)
YMRS (Young Mania Rating Scale)
MADRS (Montgomery-Asberg Depression Rating Scale)

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.

We don’t anticipate any risk from the procedures themselves, aside from those mentioned in section 7a i.

c. Use of Deception in the Study

NA

d. Use of Audio and Video Recordings

We will be video and audio record study participants during the consent process and 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 video consent form attached in section 13

e. Alternative Procedures or Courses of Treatment

Participants with insurance could alternatively receive traditional rTMS.

f. 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 6 months after the last participant completes their visit.

3. 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 treatment 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).

b. Findings from Past Animal Experiments

NA

4. DEVICES USED IN THE STUDY

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

Investigational Device 1	
Name:	MagPro X100 by MagVenture
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:	3T UHP MRI
Description:	MRI
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.

5. DISINFECTION PROCEDURES FOR MEDICAL EQUIPMENT USED ON BOTH HUMANS AND ANIMALS

NA

6. PARTICIPANT POPULATION

a. Planned Enrollment

We will recruit 60 participants only at Stanford to receive the accelerated theta burst protocol.

b. Age, Gender, and Ethnic Background

We will recruit 60 participants aged 18-80, all gender and ethnic backgrounds.

c. Vulnerable Populations

We will not include children, pregnant women, decision 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 insure all safety measures are taken for these participants.

We will not include any patients with shrapnel or any ferromagnetic within the head.

d. Rationale for Exclusion of Certain Populations

Women and minorities are included. Children are not because they are typically excluded from rTMS studies.

e. Stanford Populations

Employees and students may sign up for this study, but we will not include lab personnel due to HIPAA.

f. Healthy Volunteers

NA

g. Recruitment Details

Patients will be recruited through the outpatient clinic in the Psychiatry department at Stanford University, 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 will also use the Stanford Research Registry 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.

Flyers, Facebook, Brochures, audio, and social media tools will be used to advertise the study and recruit participants.

h. Eligibility Criteria

i. Inclusion Criteria

- Male or female, 22 to 80 years of age.
- Able to provide informed consent.
- Diagnosed with Major Depressive Disorder (MDD) and currently experiencing a Major Depressive Episode (MDE).
- Participants may currently be on a stable and adequate dose of SSRI antidepressant therapy. Participants may choose to not be on antidepressant therapy for the study duration, or to be switched from other classes to a medication from the SSRI class.
- Participants may also have a history of intolerance to at least 2 antidepressant medications. These patients with the intolerance history will not be required to be currently taking an antidepressant medication.
- Participants must qualify as "Moderately Treatment Refractory" or "High Treatment Refractory" using the Maudsley staging method.
- Meet the threshold on the total HAMD17 score of >/=20 at both screening and baseline visits (Day -5/-14 and Day 0).
- Meet the threshold on the total MADRS score of >/=20 at both screening and baseline visits (Day -5/-14 and Day 0).
- Meet the threshold on the total BDI-II score of >/=20 at both screening and baseline visits (Day -5/-14 and Day 0).
- In good general health, as ascertained by medical history.
- If female, a status of non-childbearing potential or use of an acceptable form of birth control. The form of birth control will be documented at screening and baseline.
- Concurrent hypnotic therapy (e.g., with zolpidem, zaleplon, melatonin, or trazodone) will be allowed if the therapy has been stable for at least 4 weeks prior to screening and if it is expected to remain stable.

ii. Exclusion Criteria

- Female of childbearing potential who is not willing to use one of the specified forms of birth control during the study.
- Female that is pregnant or breastfeeding.
- Female with a positive pregnancy test at participation.
- Total HAMD17 score of < 20 at the screen or baseline visits.
- Total MADRS score of < 20 at the screen or baseline visits.
- Total BDI-II score of < 20 at the screen or baseline visits.

- Current diagnosis of a Substance Use Disorder (Abuse or Dependence, as defined by DSM-IV-TR), with the exception of nicotine dependence, at screening or within six months prior to screening.
- Current diagnosis of Axis I disorders other than Dysthymic Disorder, Generalized Anxiety Disorder, Social Anxiety Disorder, Panic Disorder, Agoraphobia, or Specific Phobia (unless one of these is comorbid and clinically unstable, and/or the focus of the participant's treatment for the past six months or more).
- History of schizophrenia or schizoaffective disorders, or any history of psychotic symptoms in the current or previous depressive episodes.
- Any Axis I or Axis II Disorder, which at screening is clinically predominant to their MDD or has been predominant to their MDD at any time within six months prior to screening.
- Considered at significant risk for suicide during the course of the study.
- Cognitive impairment (as noted by previous diagnoses-including dementia).
- Has a clinically significant abnormality on the screening examination that might affect safety, study participation, or confound interpretation of study results.
- Participation in any clinical trial with an investigational drug or device within the past month or concurrent to study participation.
- Any current or past history of any physical condition which in the investigator's opinion might put the subject at risk or interfere with study results interpretation.
- History of positive screening urine test for drugs of abuse at screening: cocaine, amphetamines, barbiturates, opiates.
- Current (or chronic) use of opiates.
- History of epilepsy.
- History of rTMS exposure.
- History of any implanted device or psychosurgery for depression.
- Any history of ECT (greater than 8 sessions) without meeting responder criteria
- History of shrapnel or metal in the head or skull.
- "Low Treatment Refractory" using the Maudsley staging method.
- History of cardiovascular disease or cardiac event.
- History of OCD.
- History of autism spectrum disorder.
- History of intractable migraine
- History of independent sleep disorder.

i. Screening Procedures

Patients will undergo a screening time period where their eligibility will be confirmed. This may occur any time prior to the baseline time period. Following screening informed consent, clinical interviews and behavioral testing will occur at the Stanford Psychiatry department. The clinical interview will include a screen for inclusion and exclusion criteria, MRI safety, TASS, medical and psychiatric history, neurological exam, urine tox screen, pregnancy test, and motor threshold (see Motor Threshold section for details below).

Diagnosis will be confirmed with the MINI and/or SCID. We will also request

medical records to confirm information collected during the screening visit. Patients will be staged using the Maudsley staging method and a trained rater will perform: HAMD-21, MADRS, ATHF, YMRS and SSI.

Patients will fill out self-reports including the BDI-II, QIDS, C-SSRS, Life Stressors Questionnaire, Trauma History Questionnaire, and MCMI.

j. 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.

k. Payments to Participants

Payment will be given for participation according to the following schedule and amounts (to be paid in full at the end of participation in the study):

We will cover parking costs for the screening visit.

$50 Baseline visit
$50 Immediate post-treatment visit
$50 1 month visit

Additional bonuses:
$100 completion bonus (for not missing any follow-up appointments, completing all self-reports, and arriving on time to all study visits)

$125 EEG completion bonus ($25/day for 5 days during blinded treatment week). This does not include the optional sleep study EEGs.

Each of the above 3 visits takes ~6 hours to complete (approximately $10 per hour). Compensation would not place undue pressure to volunteer for the study.

l. Costs to Participants

None.

m. Planned Duration of the Study

Approximately 6 months from the last date of participation.

7. RISKS

a. Potential Risks

i. Investigational devices

Mania/hypomania and/or seizure.

Currently, no known cases of either risk in iTBS according to a review in The Journal of Nervous and Mental Disease (Rachid 2017).

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).

FDA approved rTMS has a 1:30,000 chance of seizure.

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.

ii. Investigational drugs

NA

iii. Commercially available drugs, biologics, reagents or chemicals

NA

iv. Procedures

Mania/hypomania and/or seizure.

v. Radioisotopes/radiation-producing machines

NA

vi. Physical well-being

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

vii. Psychological well-being

Participants will be placed in a relaxing environment. We do not anticipate that there would be any worsening.

viii. Economic well-being

Participant's economic well-being may benefit from the intervention, as they may receive an intervention that would normally cost thousands of dollars in the clinic and is not covered by most insurers.

ix. 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.

x. 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

NA

c. Procedures to Minimize Risk

We will have a trained rTMS treater in the room at all times monitoring for changes in level of consciousness. 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 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 (a 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 any participant displays an increased YMRS score (>/=2 points) on 2 questions, stimulation will be stopped to prevent any possibility of inducing hypomania or mania. 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 monitoring board (PD).

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

The Protocol Director.

iii. Frequency of DSMB meetings

NA

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

NA

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

NA.

8. 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.

9. 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.