



THE ROLE OF INDIVIDUALIZED TARGETING IN ACCELERATED INTERMITTENT THETA-BURST STIMULATION FOR DEPRESSION

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1. Background and Significance

Techniques for modulating human brain networks are rapidly evolving. One of the most exciting new developments is accelerated intermittent theta burst stimulation (iTBS), a transcranial magnetic stimulation (TMS) protocol that involves multiple daily treatments rather than gold standard once daily treatment. A specific accelerated iTBS protocol called Stanford Neuromodulation Therapy (SNT) has shown rapid and robust antidepressant effects in patients with treatment-resistant depression, leading to an FDA Breakthrough Device Designation. In an open-label study (n=21), SNT significantly reduced depression in one day and yielded 90.5% remission after five days¹. This remission rate is nearly double that of electroconvulsive therapy in the same patient population². Similar results prompted a randomized controlled trial (n=29) to be halted when a planned interim analysis demonstrated a large effect size (Cohen's $d > 0.8$) for active (79% remission) versus sham (13% remission) SNT³. These results argue against equipoise, posing unique challenges for future SNT trials.

Several issues may impact the development and scalability of SNT: 1) SNT has only been tested at a single site in a small number of patients, 2) SNT has never been tested without neuronavigation and individualized targeting based on resting-state functional connectivity (rs-fc), neither of which are widely available, and 3) There are no data on treatment target engagement.

SNT is a potential breakthrough treatment that differs from traditional TMS in several ways. Individualized targeting is a costly and complex difference that could limit development and scalability of SNT, which is being tested by a group outside of Stanford for the first time. Our group in the Center for Brain Circuit Therapeutics has the infrastructure and the expertise necessary to address these limitations. In this pilot trial, patients with treatment-resistant depression (n=40) will be randomized to one of two active treatment arms: 1) Standard SNT with neuronavigation and individualized rs-fc targeting, or 2) Modified SNT with neuronavigation and sham individualized rs-fc targeting (i.e. traditional TMS targeting based on Beam F3 method).

Another form of individualized treatment targeting that has been proposed is Neuro-Cardiac Guided TMS (NCG-TMS)⁴, where the TMS treatment target is identified as the area in the left frontal cortex where the heart rate (HR) decelerates the most when applying rTMS. This

targeting strategy was proposed after several studies reported HR deceleration during stimulation of the left DLPFC with rTMS⁵. Importantly, HR deceleration during rTMS treatment sessions have been correlated with clinical improvements^{4,5}.

Data suggest that a connection between the left DLPFC and autonomic nervous system exists, and that HR changes may be used as a guide for personalized TMS targeting without the need for an fMRI. However, studies using NCG-TMS have been limited and the precise relationships between treatment response, changes in parasympathetic tone with rTMS treatment, and left DLPFC functional connectivity to regions in the central autonomic network including the sgACC have not been determined. Lastly, while changes in parasympathetic tone have been correlated with once daily TMS treatment response, it is not known whether changes in parasympathetic tone are correlated with treatment response when multiple treatments are administered per day (as in accelerated TMS protocols)⁴⁻⁶.

Demonstrating whether clinical response correlates to TMS associated HR changes and proximity of the TMS target to the NCG-TMS DLPFC target will provide evidence for larger treatment studies prospectively using NCG-treatment targeting as well as clarify if concordance exists between fMRI guided and NCG-TMS targeting approaches⁴⁻⁶.

There was no way to run a power calculation for this study because no prior study has compared accelerated iTBS with real versus sham individualized targeting. The effect size that we seek to calculate is a real-world estimate of the clinical value of individualized targeting in accelerated iTBS protocols for depression. The results will also validate our depression network with causal information from the most robust TMS protocol available. Overall, this study is critically important for informing future accelerated iTBS trials that may shape the future of neuromodulation.

2. Specific Aims and Objectives

Aim 1: Estimate the effect size of real versus sham individualized targeting for the antidepressant effects of accelerated iTBS

Hypothesis: The antidepressant effects of accelerated iTBS with real individualized targeting will exceed the antidepressant effects of accelerated iTBS with sham individualized targeting.

Aim 2: Investigate the relationship between stimulation site and treatment response in patients receiving accelerated iTBS with sham individualized targeting

Hypothesis: Antidepressant efficacy of accelerated iTBS with sham individualized targeting will correlate with the distance between our optimal target (i.e., the area most functionally connected to our depression network) and the actual treatment site.

Aim 3: Replicate the open-label response rate of SNT

Hypothesis: The antidepressant effects of accelerated iTBS with real individualized targeting will match those from a prior open-label trial¹.

Secondary Aims and Outcomes:

Aim 4: Determine whether clinical improvement in patients with TRD receiving accelerated TMS treatment correlates with changes in parasympathetic activity (heart rate decelerations and increases in heart rate variability) during TMS treatment

Hypothesis: Greater changes in parasympathetic activity (greater HR decelerations and HRV) will correlate with improved clinical response to TMS and physiological changes that occur with rTMS will remain stable throughout the treatment course, with greater changes in parasympathetic activity (larger HR decelerations and increased HRV) during the first treatment correlating with better treatment outcomes.

Aim 5: Determine whether clinical improvements are correlated with proximity of the treatment target to the NCG-TMS target

Hypothesis: greater clinical improvements will be correlated with greater proximity of rTMS treatment target to the NCG-TMS localized region

Aim 6: Determine the functional neuroanatomy associated with heart rate decelerations that occur when iTMS treatment is administered over the DLPFC

Hypothesis: Heart rate decelerations are greater when there is greater negative functional connectivity (anti-correlations) between the region localized with the NCG-TMS procedure and the sgACC.

3. General Description of Study Design

Overview: This protocol will largely be a replication of the published SNT randomized controlled trial³, with some modifications based on unpublished clarifications as well as an ongoing SNT trial. Patients with treatment-resistant major depressive disorder (n=40) will be randomized to receive accelerated iTBS (10 treatments per day) for 5 days using either: 1) Standard SNT with neuronavigation and individualized rs-fc targeting, or 2) Modified SNT with neuronavigation (i.e., traditional TMS targeting using Beam F3 method⁴). Treatment-resistance will be defined by the Maudsley Staging Method^{5,6} [range 7-13], which aligns with prior iTBS⁷ and SNT trials^{1,3}. All patients will receive active stimulation, which will facilitate enrollment and eliminate ethical concerns about placebo treatment in a vulnerable patient population when there is existing evidence of treatment efficacy. Patients, treating technicians, and evaluating physicians will be blind to group assignment, and blind integrity will be assessed. All patients will undergo MRI scans before and after treatment as well as at a one-month follow-up appointment.

Neuroimaging: Neuroimaging data will be acquired in the Brigham and Women's Research Imaging Core on a 3T scanner. The full MRI protocol will be approximately 60-minutes, although it is possible that a protocol could run over this time.

NCG-TMS localization procedure: 90 seconds of iTBS is delivered to 4 different cortical locations on the left cortex: Beam F3, F5, FC5, and the individualized fMRI target while collecting ECG and respiration data co-registered in real time with the TMS pulses. Stimulation at each site will be flanked by 1 minute of ECG and respiration data collection. Between every location, the participant will have a resting period of 1–2 minutes to allow the HR to stabilize. The area with the largest HR deceleration during iTBS stimulation is considered the NCG-TMS localized region/target.

Physiological Measures: ECG and respiration data will be acquired using a Powerlab DAQ System on a laptop equipped with LabChart Data Acquisition Software. The ECG will be used to quantify heart rate (HR) as well as HRV indices. For each recording session, mean HR (RR intervals) and the slope of the RR-interval data will be calculated, as measure of RR interval change against time. The standard deviation of the NN (RR) intervals (SDNN) and root mean square of the successive differences (RMSSD) will be calculated within the time domain. The spectral high frequency (HF) component will be calculated within the frequency domain.

Feasibility: Patients will be recruited from outpatient psychiatric services throughout Mass General Brigham, including but not limited to mood disorders clinics and TMS clinics. This trial will leverage the robust outpatient TMS service in the Center for Brain Circuit Therapeutics at Brigham and Women's Hospital. Our service is staffed by neurologists and psychiatrists with TMS expertise, a pool of TMS technicians, and a full administrative staff. Resources include three treatment rooms, three MagVenture MagPro R30 systems, one MagPro X100 system, approximately a dozen TMS coils, Polaris Vega and Vicra cameras for use with Localite neuronavigation system, and wall-mounted videoconferencing equipment for remote patient check-ins and monitoring. We are also one of the few services in the world with an Axilum TMS-Cobot 2, which offers precise, touchless, MRI-guided robotic TMS. Finally, our TMS service is co-located with the BWH Research Imaging Core, which will be used to derive TMS targets based on each patient's individualized connectivity¹².

4. Subject Selection

Inclusion/exclusion criteria will mirror those for the published SNT randomized controlled trial³.

Inclusion Criteria

- Age 22-80
- English proficiency sufficient for informed consent, questionnaires/tasks, and treatment
- Primary diagnosis of major depressive disorder per DSM-V criteria (MINI International Neuropsychiatric Interview/ Structured Clinical Interview for DSM-5)
 - >20 on Beck Depression Inventory (BDI)
 - >20 on the Montgomery-Åsberg Depression Rating Scale (MADRS)^{13, 14}
 - Moderate to severe level of treatment resistance (Maudsley Staging Method^{10, 15})
- Stable antidepressant medication regimen, or remain medication free, for 4 weeks prior to treatment and to remain on this regimen throughout the study until the 1 month post-treatment visit.
- Primary clinician (e.g. psychiatrist, therapist, psychologist, APRN, PA, etc.) responsible for psychiatric care before, during, and after the trial
- Agreement to lifestyle considerations
 - Abstain from becoming pregnant from screening to one-month after treatment (the MRI visit)
 - Continue usual intake patterns of caffeine- or xanthine-containing products (e.g. coffee, tea, soft drinks, chocolate) throughout treatment
 - Abstain from alcohol, tobacco, and recreational drugs for at least 24 hours before the start of each MRI and TMS session

Exclusion Criteria

- Active pregnancy as determined by a urine pregnancy test
- Primary psychiatric diagnosis other than major depressive disorder requiring treatment other than comorbid anxiety disorder
- Those who did not respond to electroconvulsive therapy (ECT) after 8 sessions
- Recent (within 4 weeks) or concurrent use of rapid acting antidepressant agent (ketamine/esketamine/ECT)
- Receiving or planning to receive other TMS treatments during course of participation
- History of:
 - Prior exposure to TMS
 - Neurosurgical intervention for depression
 - Autism spectrum disorder
 - Intellectual disability
 - Severe cognitive impairment
 - Significant neurological illness (e.g., dementia, Parkinson's, Huntington's, brain tumor, seizure disorder, subdural hematoma, multiple sclerosis, brain lesion)
 - Untreated or insufficiently treated endocrine disorder
 - Treatment with investigational drug or intervention during the study period
- Depth-adjusted TMS treatment dose > 65% maximum stimulator output
- $\geq 30\%$ change in MADRS score between screening and baseline
- Anyone presenting with:
 - Mania or hypomania
 - Psychosis
 - Active suicidal ideation or a suicide attempt (defined by C-SSRS) within the past year
 - Neurological lesion
 - Contraindications to either TMS or MRI (e.g., metallic implants, severe insomnia > 4 hours per night with hypnotic, etc.).
 - Current moderate or severe substance use disorder or demonstrating signs of acute substance withdrawal
- Positive urine drug screen for illicit substances
- Existing tinnitus (ringing in the ears)
- Severe borderline personality disorder
- Any other condition deemed by the PI to interfere with the study or increase risk to the participant

Recruitment

Location: Recruitment will occur through Brigham & Women's Hospital, MGB facilities, local clinics, social medial advertisements, and public spaces in Boston (e.g., flyers and local media).

Participants: Adults aged 22-80 with depression may be screened (including those referred for clinical TMS). We will also recruit from the Research Patient Data Registry (RPDR), Rally, flyers, and social media advertising.

Procedure: Clinicians caring for patients with depression will be informed about the study and asked to refer appropriate candidates. Flyers may be posted in outpatient clinic waiting rooms at MGB facilities, local clinics, Boston area colleges, and other public spaces in the community. The study may be posted on the Mass General Brigham Rally website. We may use the RPDR to identify candidate participants who will be notified through personalized letters in Patient Gateway. We expect candidates to contact us from our listing on Clinicaltrials.gov. Additionally, we may place advertisements through social media.

Equitable recruitment procedures: Depression is more common among women and minorities. Thus, we anticipate adequate recruitment of women and minorities.

5. Subject Enrollment

Prospective participants will be pre-screened online via REDCap survey and/or phone screening. Individuals who are likely to meet study criteria will be invited to schedule a virtual or in-person screening visit. At this screening visit, a licensed physician will review the virtual consent form in detail. A virtual consent form will be available in REDCap, and an in-person consent form will also be available. No additional screening procedures will occur unless and until the prospective participant signs the consent form. At that point, the physician will cosign the consent form. Once written consent is obtained, then the remainder of the visit may be conducted by study staff.

Children are not eligible for this trial, nor are participants who do not speak and understand English. Unfortunately, our task batteries have not been validated in languages other than English.

We will not enroll participants who require surrogate decision makers because of the complexity of the trial and concerns about informed consent.

There will be no undue influence to enroll in the trial. All participants will be aware that they might qualify for traditional TMS as part of our clinical program. We will not limit time for consent.

Randomization will be outlined in the following section.

6. STUDY PROCEDURES

Overview

This protocol will largely be a replication of the published SNT randomized controlled trial³, with the exception that we are comparing individualized rs-fc targeting to traditional TMS targeting and the addition of ECG and respiratory monitoring and NCG-TMS localization.. Patients with treatment-resistant depression (n=40) who meet inclusion criteria and consent to treatment will be randomized to receive accelerated iTBS for 5 days using either: 1) Standard SNT with neuronavigation and individualized rs-fc targeting, or 2) Modified SNT with neuronavigation and individualized rs-fc targeting (i.e., traditional TMS targeting using Beam F3 method⁴). Treatment-resistance will be defined by the Maudsley Staging Method^{8,9}, [range 7-13], which aligns with prior iTBS¹⁰ and SNT trials^{1,3}. All patients will receive active stimulation, which will facilitate enrollment and eliminate ethical concerns about placebo treatment in a vulnerable patient

population when there is existing evidence of treatment efficacy. Patients, evaluating physicians, and treating technicians will be blind to group assignment, and blind integrity will be assessed. All patients will undergo MRI scans before and after treatment as well as at a one-month follow-up appointment.

Parking vouchers or transportation reimbursement will be provided for all on-site days, and lunch will be provided for each of the five treatment days. Additionally, participants will be reimbursed for pre- and post-study visits (see below).

Pre-Screening

As outlined above, all prospective participants will be pre-screened online via REDCap survey and/or phone screening.

Screening Visit

Individuals who are likely to meet study criteria will be invited to schedule a virtual or in-person screening visit. At this screening visit, a licensed physician will review the virtual or hard-copy consent form in detail. If participants choose to sign consent and enroll, then the licensed physician will administer the MADRS. The licensed physician or a trained research assistant will then administer the C-SSRS, YMRS, MINI International Neuropsychiatric Interview/Structured Clinical Interview for DSM-5 or QuickSCID-5, BAI, and BDI. Research assistants will be trained to administer all instruments/questionnaires except for MADRS. Training is provided by a licensed physician and/or electronic learning materials provided by the instrument manufacturer(s).

Baseline Visit(s)

Participants will be asked to come for an in-person pre-treatment visit in the Center for Brain Circuit Therapeutics in the Hale Building for Transformative Medicine at 60 Fenwood Road. This visit may be conducted over two or more visits based on scheduling constraints and participant preference.

Drug and Pregnancy Testing

Prospective participants will be required to submit a urine sample to test for drug use and pregnancy. Those who do not produce a negative urine drug screen and a negative urine pregnancy test, if biologically female, will be excluded from further participation.

A licensed physician will administer MADRS. If there is a $\geq 30\%$ change in MADRS score between screening and baseline the participant will be excluded from further participation.

Neuroimaging

Neuroimaging data will be acquired in the Brigham and Women's Research Imaging Core on a 3T scanner. The full MRI protocol will be approximately 60-minutes, although it is possible that a protocol could run over this time.

Task and Questionnaire Battery

- Adult Temperament Questionnaire
- Anxiety Sensitivity Index
- Barratt Impulsiveness Scale
- Adult ADHD Self-Report Scale
- Behavior Rating of Executive Function
- Emotion Reactivity Scale
- Patient Global Impressions Survey
- Young Mania Rating Scale (YMRS)
- Scale for Suicide Ideation
- Computerized version of TCI-R140 (Temperament and character inventory, revised 140-question format)
- A multidimensional task-based emotional assessment (includes interactive testing which is not available in attachable form. In lieu of this, we are attaching publications that describe the assessment)
- A paced breathing task
- Patient-Health Questionnaire-15 (PHQ-15)

Randomization

Participants will be randomized to neuronavigation to functional connectivity target or neuronavigation to Beam F3 target. Clinical assessments will be administered by a rater who is also blinded to the participant's group assignment unless there is a clinical reason to break the blind. Treating technicians will also be blinded to participant's group assignment; someone who is not delivering treatment will be in charge of randomization and delivery of appropriate coordinates for neuronavigation.

Participants will also be randomized to the order of neurocardiac guided target stimulation and the order of breathing pace in the paced breathing task using Research Randomizer developed by Geoffrey C. Urbaniak and Scott Plous¹⁶

Treatment Preparation

Participants will put on a swimming cap and, their resting motor threshold (intensity of magnetic pulse required to produce a motor contraction 50% of the time that pulses are delivered) will be assessed by administering several individual magnetic pulses over the left motor cortex. The locations of the appropriate part of the motor cortex will be initially estimated as approximately 2 cm lateral to the vertex of the head, and the location/intensity of stimulation will be titrated until a contraction is observed in the contralateral abductor pollicis brevis (APB) muscle. All participants will also undergo 90 seconds of TMS at each identified NCG-TMS site (4 sites total) while they are physiologically monitored with a respiration belt and ECG. All individuals will get treated at one of two treatment sites: 1) Their individualized target based on fMRI data (Localite GmbH, Sankt Augustin, Germany)¹⁴, and 2) Beam F3 target¹⁷.

Treatment Visits

TMS treatments will be administered on the BWH TMS Service. All TMS treatments will be delivered with a MagVenture MagPro X100 system (MagVenture A/S, Denmark) equipped with

a Cool-B65 coil. A Localite neuronavigation system (Localite GmbH, Sankt Augustin, Germany) will be used to navigate to the randomized target.

Prior to initiation of treatment, resting motor threshold (intensity of magnetic pulse required to produce a motor contraction) will be assessed by administering several individual magnetic pulses over the left motor cortex. The locations of the appropriate part of the motor cortex will be initially estimated as approximately 2 cm lateral to the vertex of the head, and the location/intensity of stimulation will be titrated until a contraction is observed in the contralateral abductor pollicis brevis (APB) muscle approximately 50% of the time that pulses are delivered.

TMS will be administered to the appropriate treatment site. We aim to deliver 10 iTBS treatment sessions per day (18,000 pulses/day) for 5 consecutive days (90,000 pulses total). In the unlikely event that a participant misses an hourly treatment, then they will receive the next treatment on schedule. Each iTBS treatment consists of 60 cycles of 10 bursts of three pulses at 50 Hz delivered in 2-second trains (5 Hz) with an 8-second intertrain interval. Stimulation will be delivered at 90% resting motor threshold (rMT), which is lower than the 120% of standard daily iTBS treatment. The rMT will be adjusted for depth of the identified functional connectivity target. The personalized targets created for each individual in the real rTMS group will be located at varying cortical depths. Since the strength of the induced electric field decreases with increasing distance from the TMS coil, depth-corrected intensities will be used with the aim of delivering the equivalent of 90% of rMT to all individualized targets. For safety, stimulation intensity will never exceed 120% of rMT. We may also collect heart rate data in between treatment visits and repeat the paced breathing tasks.

Our primary endpoint scale, MADRS, will be administered at screening, immediately before treatment begins (baseline visits or Day 1 of treatment) and immediately after treatment ends (Day 5 of treatment or 1 week follow-up visit). BDI and YMRS will be administered daily throughout treatment.

There will always be a licensed physician on-site and immediately available.

Follow-Up Visits

Post-Treatment Week 1 (in-person). Participants will return to the Center for Brain Circuit Therapeutics for an MRI scan (see above) as well as repeat MADRS with a licensed psychiatrist. In the event of scheduling issues, the MRI will be conducted as close to 1 week post-treatment as possible. We will also collect BDI, YMRS and PHQ-15. The participant will complete 20 minutes of ECG and respiratory monitoring.

Post-Treatment Month 1 (in-person). Participants will return to the Center for Brain Circuit Therapeutics for an MRI scan (see above) as well as a repeat MADRS with a licensed psychiatrist. We will also collect BDI, BAI, and YMRS. Finally, the patient will complete the task battery from the baseline visit and complete 20 minutes of ECG and respiratory monitoring.

Post-Treatment Month 3 (link). Participants will receive a link to complete the BDI, BAI, and YMRS. These data will be collected in REDCap. We will not follow up on changes in these scales, as patients have primary physicians following them longitudinally.

Post-Treatment Month 6 (link). Participants will receive a link to complete the BDI, BAI and YMRS. These data will be collected in REDCap. We will not follow up on changes in these scales, as patients have primary physicians following them longitudinally.

Post-Treatment Month 9 (link). Participants will receive a link to complete the BDI, BAI, and YMRS. These data will be collected in REDCap. We will not follow up on changes in these scales, as patients have primary physicians following them longitudinally.

Post-Treatment Month 12 (link). Participants will receive a link to complete the BDI, BAI and YMRS. These data will be collected in REDCap. We will not follow up on changes in these scales, as patients have primary physicians following them longitudinally.

Remuneration

In addition to the medical benefit derived from participation, participants will receive the following payments:

\$60 for screening visit
\$100 for baseline visit(s)
\$40 for Post-Treatment Week 1
\$80 for Post-Treatment Month 1
\$10 for Post-Treatment Month 3
\$10 for Post-Treatment Month 6
\$10 for Post-Treatment Month 9
\$10 for Post-Treatment Month 12 (plus additional \$40 bonus)

Treatments are not compensated due to receiving free treatment.

If participants do not complete the study, we will pay them for the visits they did complete.

Paid parking or up to \$150 in transportation fees.

Lunch provided during visits.

7. Risks and Discomforts

The primary side effect of concern with TMS is seizure. TMS seizures are rare. It is estimated that seizure occur in one out of every 32,000 treatments of routine daily TMS, which is similar to the incidence reported due to antidepressant medications¹⁸. There have been no seizures reported in the published SNT trials, which involve treatment below motor threshold^{1, 3}. This risk will be minimized by excluding patients at elevated seizure risk as determined by the referring physicians and supervising investigators, as well as specifically excluding patients with known seizure history

and patients with TBI subtypes associated with elevated seizure risk (penetrating injury and intraparenchymal hemorrhage). Furthermore, a board-certified neurologist and psychiatrist will be available at all times in the event that a subject requires further evaluation in the unlikely event of signs of seizures or increased seizure risk.

The risks of TMS are unknown in patients with cardiac pacemakers, patients with metallic implants within the head (including cochlear implants or other electronic devices), and pregnant patients. As a result, these patients will be excluded from the study.

Major depression is associated with risk of harm due to suicide and poor self-care. This risk is not increased by TMS treatment. To the contrary, risk of harm due to direct effects of major depression will be decreased in this study, as all participants will be evaluated routinely for suicidal ideation. A board-certified psychiatrist will be available at all times during treatment visits in the unlikely event of deterioration of a subject's psychiatric symptoms.

Tinnitus is relatively rare, especially when wearing proper hearing protection as required in this trial. Large multi-site trials do not list tinnitus as a side effect of TMS, however, there are a small amount of case reports and anecdotal reports regarding tinnitus. In the event a participant reports persisting ringing in the ears, we will re-evaluate their participation in the trial.

There are case reports of hypomania being induced in patients with a bipolar diathesis who receive daily TMS, but some of these also occur in patients receiving sham TMS. There were no reported manic symptoms in the SNT trials.

In rare cases, subjects may experience discomfort during the MRI scan due to claustrophobia and/or vibration sensitivity. There is also a small risk of discomfort if subjects have metallic tattoos or metallic implants. There is a risk of injury if participants fail to remove metallic jewelry and/or piercings prior to entering the scanner. Individuals with pacemakers or implantable cardiac defibrillators may risk malfunction of this device if they fail to report its presence. These risks will be minimized by completion of a standard BWH pre-screening MRI safety questionnaire. This will include screening for claustrophobia, vibration sensitivity, and presence of the aforementioned metallic objects.

There is a small risk of confidentiality breach in this study. These risks will be minimized by the following procedures:

1. Paper/hard copy data will be transported in a sealed, opaque envelope by study personnel and will be stored in a locked file cabinet in a locked or directly supervised office in the Medical Research Building at Brigham & Women's Hospital. Paper records will be labeled with a unique de-identified subject code.
2. All electronic data will be kept in a secure REDCap database, a Partners Dropbox Business folder, or MGB OneDrive, the latter two sites accessible only to study team members.
3. De-identified MRI data may be transported from the scanner to the laboratory via a secure FTP server containing MRI images. These electronic files will be stored in the Center for

Brain Circuit Therapeutics neuroimaging repository, access to which requires approval from BWH IT.

8. Benefits

All participants will receive a treatment with an FDA Breakthrough Device Designation for depression. They would not have access to this treatment outside of a clinical trial setting, as the treatment is not covered by insurance and is prohibitively expensive and technically complicated to administer. Thus, participants may benefit by receiving a treatment that they would otherwise be unable to access.

Furthermore, the study may benefit society. SNT is a potential breakthrough treatment that differs from traditional TMS in several ways. Individualized targeting is a costly and complex difference that could limit development and scalability of SNT, which is being tested by a group outside of Stanford for the first time. There was no way to run a power calculation for this study because no prior study has compared accelerated iTBS with real versus sham individualized targeting. The effect size that we seek to calculate is a real-world estimate of the clinical value of individualized targeting in accelerated iTBS protocols for depression. The results will also validate our depression network with causal information from the most robust TMS protocol available. Overall, this study is critically important for informing future accelerated iTBS trials that will shape the future of neuromodulation.

9. Statistical Analysis

Power Calculation. There is no way to run a power calculation for this trial because there are no published data on accelerated iTBS with real versus sham individualized targeting. It is for this reason that our first aim is focused on calculating an effect size. This effect size could help to ensure that future trials are adequately powered to detect a significant group difference in response or remission rates.

Aims and Hypotheses

Aim 1: Estimate the effect size of real versus sham individualized targeting for the antidepressant effects of accelerated iTBS.

Hypothesis: The antidepressant effects of accelerated iTBS with real individualized targeting will exceed the antidepressant effects of accelerated iTBS with sham individualized targeting.

Aim 2: Investigate the correlation between stimulation site and treatment response in patients receiving accelerated iTBS with sham individualized targeting

Hypothesis: Antidepressant efficacy of accelerated iTBS with sham individualized targeting will correlate with the distance between our optimal target (i.e., the area most functionally connected to our depression network) and the actual treatment site.

Blind Integrity. Treating technicians and participants will be asked to guess the participant's treatment allocation and to report their confidence in their guess (on a scale of 0 to 100) on the last

day of treatment. A guess metric will be created that ranges from 0% (no confidence in the binary treatment allocation response) to 100% (full confidence in the binary treatment allocation response). If not all participants indicate their confidence, then binomial tests will be used to determine whether the number of correct guesses exceed chance. Finally, linear regression analysis will be used to assess the relationship between the guess metric, confidence metric, and the change in depression severity, as indicated by percent change in MADRS score from baseline.

Outcomes: The primary outcome measure is difference between groups using Montgomery–Åsberg Depression Rating Scale (MADRS) one month after treatment, normalized to baseline. Participants will be excluded if their total MADRS score changes by 30% or more from screening to baseline assessment. Secondary outcome measures include: 1) MADRS immediately after treatment ends and 2) Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Young Mania Rating Scale (YMRS) immediately after treatment ends and at all subsequent timepoints (1, 3, 6, 9, 12 months), 3) Change in rs-fc in the depression circuit (i.e., target engagement), which may be a more objective and sensitive marker of individualized targeting compared to our clinical outcome metrics, 4) Percentage of screened patients from TMS clinical programs who select the accelerated iTBS trial (10 daily treatments for 5 days) over routine clinical TMS (once daily treatment for 5-7 weeks). 5) Change in HR and HRV indices (SDNN, RMSSD, HF power) in between treatments daily and at subsequent timepoints (week 1 and month 1). 6) Freesurfer will be used to analyze functional connectivity between the NCG-TMS localized region and the regions of central autonomic network (sgACC, insula, and amygdala) 7) A regression model will be used to assess whether proximity (measured in mm) to the NCG-TMS localized region is associated with treatment response (absolute change in MADRS).

Statistical Analyses. Statistical analyses will likely be conducted using SPSS, Excel, R, or Matlab. These analyses will model the published SNT protocol very closely. This section was adapted from the SNT trial.

As outlined above, our primary outcome measure will be the MADRS score 4 weeks after treatment, normalized to baseline. MADRS scores will be used to calculate response and remission rates in each group. Response will be defined as a reduction $\geq 50\%$ in MADRS score, and remission will be defined as MADRS score ≤ 10 . Participants will be identified as responders or remitters if they met these specific criteria at any point during the 4-week follow-up. This method was chosen rather than response or remission at a single time point to allow for different response trajectories.

As described in the SNT trial, this approach to calculating response and remission rates was chosen specifically as part of developing a rapid treatment for major depressive disorder that is bridged into a comprehensive long-term treatment to maintain participants in a state of remission. Thus, the most relevant measure of remission rates for this approach is the proportion of individuals who enter remission at any point in the month following treatment, regardless of whether they enter remission immediately after treatment or after a delayed-response trajectory, as maintenance treatment would be engaged irrespectively of treatment trajectory. Fixed effects of time, treatment group (sham versus real individualized targeting), and their interaction will be assessed. Compound symmetry covariance structure will be used for all analyses except cases in which the

models failed to converge or converged on nonreal solutions. In these cases, autoregressive covariance structures will be used. All post hoc pairwise comparisons will be Bonferroni corrected.

We will also assess differences between groups in the task battery items (outlined above). Each of these metrics will be assessed for normality using a Shapiro-Wilk test. If the distribution is normal, then the metric will be compared between groups using Student's t-test. If the distribution is non-normal, then the metric will be compared between groups using a Mann-Whitney U-test.

Adverse events:

Incidence of adverse events will be compared between active and sham individualized targeting groups via z-test for proportions.

10. Monitoring and Quality Assurance

The principal investigator will hold weekly meetings with study staff, in which adherence to the protocol will be reviewed. These meetings will include review of informed consent documents, case report form entries, source documents, and treatment records (without group labels).

All participants will be evaluated daily for adverse effects including headaches, tinnitus, worsening depression, worsening anxiety, suicidality, manic symptoms, and seizures. If any of these symptoms worsen, the patient will be evaluated by a board-certified psychiatrist or neurologist, depending on the nature of the effects. Patients will also complete a Young Mania Rating Scale (YMRS) at the end of each treatment day.

An emergent safety evaluation by a licensed physician will always occur if participants subjectively report worsening suicidal thoughts or if their daily scores on suicide subscale items include the following score cut-offs:

1. C-SSRS, answers of "Yes" to questions 4 or 5
2. BDI – Question 9, answers of 2 or 3.
3. MADRS – Question 10, answers of 4, 5, or 6.

TMS technicians administering treatment will be aware of the score cut-offs and be able to request an emergent safety evaluation. TMS technicians will also monitor for symptoms of mania, which will also initiate an emergent evaluation with a licensed physician.

In the event of a seizure or active suicidality with intent and plan, the participant will be referred for emergency care, withdrawn from the study, and reported to the IRB. Furthermore, all participants will receive regular monitoring of clinical changes/adverse effects, following the standard of care for our TMS clinic. This will include assessment of depression severity and evaluations with the clinic psychiatrist when clinically necessary. In practice, additional psychiatric and neurological evaluations are usually conducted when the patient experiences unexpected symptoms, and the psychiatrist aims to determine whether these symptoms may be related to the treatment.

11. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☐ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐ Additional privacy and/or confidentiality protections

12. References

1. Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C *et al.* Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression. *Am J Psychiatry* 2020; **177**(8): 716-726.
2. Heijnen WT, Birkenhager TK, Wierdsma AI, van den Broek WW. Antidepressant pharmacotherapy failure and response to subsequent electroconvulsive therapy: a meta-analysis. *J Clin Psychopharmacol* 2010; **30**(5): 616-619.
3. Cole EJ, Phillips AL, Bentzley BS, Stimpson KH, Nejad R, Barmak F *et al.* Stanford Neuromodulation Therapy (SNT): A Double-Blind Randomized Controlled Trial. *Am J Psychiatry* 2021: appiajp202120101429.
4. Iseger TA, van Bueren NER, Kenemans JL, Gevirtz R, Arns M. A frontal-vagal network theory for Major Depressive Disorder: Implications for optimizing neuromodulation techniques. *Brain Stimul* 2020; **13**(1): 1-9.
5. Iseger TA, Padberg F, Kenemans JL, van Dijk H, Arns M. Neuro-Cardiac-Guided TMS (NCG TMS): A replication and extension study. *Biol Psychol* 2021; **162**: 108097.
6. Iseger TA, Padberg F, Kenemans JL, Gevirtz R, Arns M. Neuro-Cardiac-Guided TMS (NCG-TMS): Probing DLPFC-sgACC-vagus nerve connectivity using heart rate - First results. *Brain Stimul* 2017; **10**(5): 1006-1008.
7. Trapp NT, Bruss J, King Johnson M, Uitermarkt BD, Garrett L, Heinzerling A *et al.* Reliability of targeting methods in TMS for depression: Beam F3 vs. 5.5 cm. *Brain Stimul* 2020; **13**(3): 578-581.
8. Fekadu A, Wooderson SC, Markopoulou K, Cleare AJ. The Maudsley Staging Method for treatment-resistant depression: prediction of longer-term outcome and persistence of symptoms. *J Clin Psychiatry* 2009; **70**(7): 952-957.
9. Fekadu A, Donocik JG, Cleare AJ. Standardisation framework for the Maudsley staging method for treatment resistance in depression. *BMC Psychiatry* 2018; **18**(1): 100.
10. Li CT, Chen MH, Juan CH, Huang HH, Chen LF, Hsieh JC *et al.* Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. *Brain* 2014; **137**(Pt 7): 2088-2098.
11. Hagler DJ, Jr., Hatton S, Cornejo MD, Makowski C, Fair DA, Dick AS *et al.* Image processing and analysis methods for the Adolescent Brain Cognitive Development Study. *Neuroimage* 2019; **202**: 116091.
12. Barbieri R, Matten EC, Alabi AA, Brown EN. A point-process model of human heartbeat intervals: new definitions of heart rate and heart rate variability. *Am J Physiol Heart Circ Physiol* 2005; **288**(1): H424-435.

13. Levkovitz Y, Isserles M, Padberg F, Lisanby SH, Bystritsky A, Xia G *et al.* Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. *World Psychiatry* 2015; **14**(1): 64-73.
14. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M *et al.* Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Archives of general psychiatry* 2010; **67**(5): 507-516.
15. Fekadu A, Wooderson S, Donaldson C, Markopoulou K, Masterson B, Poon L *et al.* A multidimensional tool to quantify treatment resistance in depression: the Maudsley staging method. *J Clin Psychiatry* 2009; **70**(2): 177-184.
16. Research Randomizer (Version 4.0). <http://www.randomizer.org/>, 2013, Accessed Date Accessed 2013 Accessed.
17. Beam W, Borckardt JJ, Reeves ST, George MS. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. *Brain Stimul* 2009; **2**(1): 50-54.
18. Taylor JJ, Newberger NG, Stern AP, Phillips A, Feifel D, Betensky RA *et al.* Seizure risk with repetitive TMS: Survey results from over a half-million treatment sessions. *Brain Stimul* 2021; **14**(4): 965-973.