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

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9. STATISTICAL CONSIDERATIONS

Primary Mechanistic Objective and Relevant Clinical Objective

Primary Mechanistic Objective: To determine if accelerated theta-burst stimulation can provide a rapid reduction in acute depressive symptoms in treatment resistant outpatients with MDD. **In other words, the Primary Outcome Measure** is the change in depressive mood in active left DLPFC versus sham left DLPFC iTBS arms.

Relevant Clinical Objective: To determine the effect of active, accelerated theta-burst stimulation over the left DLPFC on decreasing depressive symptoms as measured by a change in the *Montgomery-Asberg Depression Rating Scale (MADRS).*

Relevant Clinical Hypothesis: Active accelerated theta-burst stimulation over the left DLPFC will significantly reduce depressive symptoms in treatment resistant outpatients with MDD compared to sham.

Secondary Objectives

Secondary Objective A: To explore whether accelerated theta-burst stimulation over the left DLPFC results in functional connectivity differences between the left DLPFC and the anterior cingulate cortex (ACC) using functional magnetic resonance imaging (fMRI).

Secondary Hypothesis A: Active accelerated intermittent theta-burst stimulation over the left DLPFC will modulate neural circuitry and thus change brain activity by decreasing functional connectivity between the left DLPFC and ACC.

Secondary Objective B: To explore whether accelerated theta-burst stimulation over the left DLPFC results in changes in heart rate variability using electrocardiogram (ECG) recordings.

Secondary Hypothesis B: Active accelerated theta-burst stimulation over the left DLPFC will result in increased heart rate variability compared to sham.

Secondary Objective C: To explore whether accelerated intermittent theta-burst stimulation over the left DLPFC leads to changes in depression symptoms as assessed by the Hamilton Depression Rating Scale 17-item (HAM-17) and Hamilton Depression Rating Scale 6-item (HAM-6).

Secondary Hypothesis C: Active accelerated intermittent theta-burst stimulation over the left DLPFC will lead to decreased scores on the HAM-17 and HAM-6 compared to baseline, indicating decreased depression symptomatology.

General Design Issues

Statistical Hypotheses: We will examine the effect of active aiTBS on the functional connectivity between left DLPFC and dACC as compared to sham aiTBS. In the *Relevant Clinical Hypothesis*, we will examine the effect of active aiTBS on reducing depressive symptoms in treatment resistant outpatients with MDD as assessed by the MADRS. In *Secondary Hypothesis B*, we will explore whether aiTBS over the left DLPFC results in changes in heart rate variability using electrocardiogram (ECG) recordings. Additionally, we will also examine the effect of active aiTBS on reducing depressive symptoms as measured by the HAM-17 and HAM-6 (*Secondary Hypothesis C)*.

Rationale for Study Design: The randomized, triple-blind, counterbalanced, mechanistic clinical trial design allows for the most definitive assessment of the feasibility of modulating the neural circuitry underlying depression with accelerated intermittent theta-burst stimulation (aiTBS) along with the measuring the effects of this neuromodulation strategy on the underlying neural circuitry. The same subjects are utilized for all three MRI scan sessions, that is, for the pre-aiTBS scan session, the immediate post-aiTBS scan session and for the 1-month post-aiTBS follow-up scan session (to address functional connectivity aims). The rationale for using the same subject three times is to enable analysis of functional connectivity differences in the left DLPFC and dACC in response to aiTBS across time. The order will be counterbalanced and the two groups (aiTBS versus sham) will be cross-sectionally compared, treating the contrast (baseline vs post aiTBS) as one univariate outcome, which is customary in imaging studies.

Sample Size and Randomization

The study will be powered for an estimated effect size of Cohen's d=0.8 for change in Montgomery-Åsberg Depression Rating Scale (MADRS) between sham and active rTMS groups from baseline to 1-month following the end of treatment. We will set the probability of rejecting a true null hypothesis (Type 1 error, alpha) at 0.05 (two-sided). Prior investigations of iTBS of the L-DLPFC for treatment resistant depression reported an effect size of d=1.337, leaving our estimate conservative. This study will aim to recruit 60 individuals assuming approximately 10% missing data due to unusable imaging data and dropouts. Our longitudinal analyses will be conducted fully utilizing data that will be collected across all time points (baseline, aiTBS (days 1-5), and post-aiTBS, which will inform clinical and exploratory analyses. Thus, assuming independent groups and ~10% attrition, we aimed to recruit 30 participants in each treatment group, active or sham rTMS. We plan to conduct an interim analysis after 30 participants complete the 1-month post-time point to assess for futility, inferiority or superiority of the active compared to sham rTMS treatments. Feasibility analyses (e.g., acceptance, adherence, focus group data) will be conducted based on descriptive-level statistics to guide future adaptations and refinements of the proposed aiTBS protocol.

Power to detect reduction in suicidality (hypothesis 1) and depressive symptoms (hypothesis 2) is based on ES estimates observed in (1) a previous RCT pilot rTMS for pre-treatment to post-treatment symptom change in HAMD (d>1), and (2) two sham-controlled TBS trials, utilizing a similar treatment approach, which demonstrated large effects for both suicidal ideation and depressive symptoms (d>1). Given this information, we used a somewhat conservative effect size of d=0.8 for our power analyses. Under this setting, a minimum of n= 30 per group would be

needed to achieve power of .8 to detect significant reductions in suicidal ideation/antidepressant responses achieved by each coil.

In terms of power to detect non-inferiority across left DLPFC and ACC coils, the only previous study (to our knowledge) which has investigated differences in depressive symptom changes associated with the stimulation of different brain regions, showed that 50 participants in each group (each stimulation site) was sufficient in order to detect differences in symptom changes across different stimulation sites (106). Therefore, n=100 was determined to be a sufficient sample size to investigate differences in ACC and left DLPFC stimulation.

As our study is a randomized controlled study, in line with the intention to treat principle, our primary analysis will be a straightforward comparison of the active versus sham groups using a linear model. Following the convention in rTMS studies, we will conduct our primary analyses treating the contrast (baseline MADRS score vs immediate post-aiTBS MADRS score) as one univariate outcome. The univariate model described below can be estimated either using linear regression or analysis of variance procedures.

A continuous outcome Y for individual i (i=1,2,3…., N) can be expressed as
$Y_i = \alpha + \gamma Z_i + \varepsilon_i$, where α is the mean of the sham group, Z_i is the randomized treatment assignment status (0=sham, 1=active), γ is the treatment effect, and $\varepsilon_i \sim N(0, \sigma^2)$. According to random assignment, the estimate of γ will be interpreted as causal effect of treatment assignment.

We do not expect much variation across our narrowly defined subjects, although some variation is still possible. As a way of sensitivity analysis, we will also analyze the data in the linear mixed effects modeling framework allowing for random intercepts, although this is not customary in imaging studies. The linear mixed effects model described below will be estimated using the maximum likelihood estimation method implemented in SPSS or in Mplus.

The outcome Y for individual i at time point t (t = 1,2 for pre and post) is now expressed as

$$Y_{it} = \eta_{0i} + \eta_{1i} W_t + \varepsilon_{it}, \quad (2)$$
$$\eta_{0i} = \eta_0 + \gamma_0 Z_i + \zeta_{0i} \quad (3)$$
$$\eta_{1i} = \eta_1 + \gamma_1 Z_i + \zeta_{1i} \quad (4)$$

where η_{0i} is the initial status and η_{1i} is the linear growth. The set of time scores W_t reflects the linear growth (0,1) for the pre and post assessments. The residual ε_{it} is allowed to vary across time and is assumed to be normally distributed in out parametric estimation approach. The intercepts in (3)-(4) can be interpreted as the main initial status (η_1) and linear growth (η_2) for the sham group. The random effect residual ζ_{0i} is assumed to be normally distributed, whereas ζ_{1i} is fixed at zero as we only have two time point data. The effect of treatment on initial status (γ_0) will be fixed at zero in line with the random assignment. The estimate of γ_1 will be interpreted as causal effect of treatment assignment on the pre and post change in the outcome.

Stimulation Group Assignment Procedures

Stimulation Group Assignment Procedures: Random assignment is a procedure used in experiments to create study groups with similar characteristics so that the groups are equivalent

at the beginning of the study. We perform randomization using permuted block to ensure balancing between arms.

Randomization Rationale and Procedure: The *MagLink* software program is used by the principal investigator to define the stimulation protocol for each patient enrolled in the study. This includes defining whether a given patient is to receive real or sham stimulation. When the protocol has been defined it is downloaded to a Patient Key (USB memory device) (See Magventure Cool-Coil Guide).

Maintenance of Randomization Codes: In order to use Active/Placebo (A/P) for different groups, an Excel spreadsheet with number series for operators and subjects (active stimulation as well as placebo stimulation) is stored by a separate clinical research coordinator who is trained to maintain the blind.

Maintaining Appropriate Masking: All site personnel will be masked to the stimulation group assignment (active versus sham) for each subject. Specific aspects of the trial design are intended to optimize the integrity of the masking and all staff will be trained to the procedures for masking during the site initiation visit. In addition to those procedures, the treater will be provided with individually sealed and numbered envelopes, corresponding to subject randomization numbers.

Blinding and Unblinding methods: For stimulation sessions, *MagLink* will require use of the Cool-B65 A/P coil that has a built-in position sensor used to ensure that the correct (active or sham) side of the coil faces towards the patient's head. If the coil position is wrong the operator will get a "Flip Coil" prompt on the MagPro screen. To ensure best possible blinding of patients the current stimulation provided with the Cool-B65 A/P coil should be used to stimulate the patient's skin. When a stimulation session is completed, the session data are stored on both the Patient Key and the Operator Key. Dr. Nolan Williams is authorized to break the blind.

Definition of Populations

We will compare individuals assigned to the active aiTBS condition and individuals assigned to the sham condition as randomized in line with the ITT principle. Noncompliance with aiTBS (or sham) is not expected, although in that case, we will compare groups as randomized regardless of the compliance status in line with ITT. Missing assessment due to unusable imaging data or dropout will be handled as missing at random conditional on observed information.

Interim Analyses and Stopping Rules

Because of the anticipated low level of adverse events of aiTBS and MRI, interim analysis of data, protocol and adverse events will occur by study staff at least once a year. Serious adverse events will be reviewed on a monthly basis, unless a more urgent review is requested. Only under extreme circumstances or if it were determined that a high level of side effects was due to aiTBS

and/or MRI, would the PI be charged with breaking the study mask. This study will be stopped prior to its completion if: [1] the intervention is associated with adverse effects that call into question the safety of the intervention; [2] difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; [3] any new information becomes available during the trial that necessitates stopping the study; or [4] other situations occur that might warrant stopping the study.

Data Analyses

The Primary Mechanistic Outcome Measure for this study is percent change in MADRS score at one-month post treatment. **The Relevant Clinical Outcome Measure** is a reduction in depressive symptoms in treatment resistant outpatients diagnosed with MDD, as measured by change in MADRS score. For secondary aims, the emphasis is on identifying the magnitude of effects (clinical significance, effect size) instead of statistical significance. We will test whether the change in depressive symptoms from baseline to 1-month post-treatment is greater in the active aiTBS group as compared to the sham group. Following the convention in imaging studies, we will conduct our primary analyses treating the contrast (baseline versus post) as one univariate outcome. We do not expect much variation across our narrowly defined subjects, although some variation is still possible. Given that, we will also analyze the data in the linear mixed effects modeling framework allowing for random intercepts (although this is not customary in imaging studies) as a way of sensitivity analysis.

Moderator/mediator investigation: We will explore various baseline variables as potential moderators of aiTBS. For this investigation, we will employ the MacArthur approach for moderator analysis. We will also examine potential mediators of rTMS effect using the MacArthur approach as well as contemporary causal mediation approaches, which we believe will provide valuable insights regarding the neuromodulation mechanism for the next phase of investigation.

Handling of missing data: We use the same sample twice to achieve enough statistical power with our moderate sample size, not to model the change between scanning sessions. With no longitudinal components, the two groups (aiTBS versus sham) will be cross-sectionally compared in our primary aims. The impact of missing data due to attrition is minimal. Further, time between assessments is so narrow that the probability of having cases with missing data (dropout, attrition) is very low. As a way of assessing the impact of missing scan sessions, we will repeat our main analyses treating outcomes measured in the pre-aiTBS scan and in the 1-month post-aiTBS scan as multivariate outcomes. This will allow us to include all participants in the analysis as long as two of the three scans are available. In this analysis framework, missing data will be handled assuming that it is missing at random conditional on observed scan session data (maximum likelihood estimation). Analyzing the data using both univariate and multivariate analysis approaches will also serve as sensitivity analyses. Additionally, we will include the order of scan sessions in the model to account for the carryover and order effects.