Stanford Accelerated Intelligent NeuromodulationTherapy 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 providea 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.

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.

Secondary Objectives

Secondary Objective A: To explore whether accelerated theta-burst stimulation over the left DLPFC results in functional connectivity changes between the subgenual anterior cingulate cortex (sgACC) and Default Mode Network (DMN) using functional magnetic resonance imaging (fMRI).

Secondary Hypothesis A: Active accelerated intermittent theta-burst stimulation over the left DLPFC will result in functional connectivity changes between the sgACC and the DMN.

Secondary Objective B: To explore whether accelerated intermittent theta-burst stimulation overthe 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 B: 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, indicatingdecreased depression symptomatology.

General Design Issues

Statistical Hypotheses: We will examine the effect of active aiTBS on the functional connectivity between sgACC and DMN. 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 also examine the effect of active aiTBS on reducing depressive symptoms as measured by the HAM-17 and HAM-6.

Rationale for Study Design: The design will allow to assess the feasibility of modulating the neural circuitry underlying depression with accelerated intermittent theta-burst stimulation (aiTBS) alongwith 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 scansession (to address functional connectivity aims). The rationale for using the same subject threetimes is to enable analysis of functional connectivity differences in the left DLPFC and dACC in response to aiTBS across time.

Sample Size

The study will be powered for an estimated effect size of Cohen's d=0.6 for change in Montgomery-Åsberg Depression Rating Scale (MADRS) between baseline and one month post treatment using within subject t-test. Prior investigations of iTBS of the L-DLPFC for treatment resistant depression reported an effect size of d=1.337, leaving our estimate conservative. We will set the probability of rejecting a true null hypothesis (Type 1 error, alpha) at 0.05 (two-sided) with 80% power. That will require a final sample size of 23 participants. This study will aim to recruit 30 individuals assuming approximately 20% missing data due to unusable imaging data or dropouts.

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. 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: 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.