

Official title: Elucidating Neural Mechanisms of Hypo/Mania Using Theta Burst Stimulation

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Statistical Design and Power (please main research plan for detailed references)

Aim 1: To determine the acute impact of left vIPFC cTBS on RE-related activity and FC in left vIPFC and reward circuitry in remitted BD and healthy/ non BD adults. H1. Acute cTBS over the left vIPFC will be associated with significantly greater reductions in these neural measures in all adults (vs. control and sham conditions).

Aim 2: To: a) determine if acute changes in H1 neural measures induced by cTBS over the left vIPFC are associated with acute changes in hypo/mania-related affect; and b) if negative urgency moderates these relationships. H2. Greater reductions in RE-related activity and FC in left vIPFC and reward circuitry after cTBS over left vIPFC will be associated with greater acute reductions in hypo/mania-related negative affect pre-post cTBS. These relationships will be moderated by negative urgency, given positive associations among RE-related left vIPFC activity, negative urgency, and hypo/mania predisposition, and not evident for other cTBS conditions.

Aim 3: To compare the relative effects of cTBS over the left vIPFC (vs. control and sham conditions) on neural and affect measures in BD vs. healthy/ non BD adults. H3. The magnitudes of these changes will be greater in BD vs. healthy/ non BD adults, given higher pre cTBS baseline neural measures and negative urgency in BD adults.

Analytic approach. We will examine distributions of all measures of interest to determine departures from normality, and assess for outliers. Data reduction techniques (e.g., principal components analysis) will reduce # multiple comparisons. For parametric statistical models, model residuals will be examined for assumption violations, and appropriate methods applied (e.g., transformations, non-parametric models). A Bonferroni correction will be applied to adjust statistical thresholds for multiple parallel tests.

Covariates: time variant/ invariant, as appropriate: hypo/mania, depression and anxiety severity, other response tendencies (e.g., anhedonia, trait anxiety), present/ previous psychiatric diagnoses, age of BD onset, # illness episodes, personality disorders, especially Borderline Personality Disorder, medication, psychotherapy, caffeine, nicotine, alcohol, cannabis use (below SUD levels), family psychiatric illness history, age, gender, age x cTBS condition and gender x cTBS condition, as appropriate (see below), SES, IQ, years of education, menstrual cycle phase (females, self-report), trauma history, cTBS condition order, scalp-cortex distance. Categories (self- vs. externally-related) of resting state cognitions (yes/no; resting state FC analyses). As recommended by the Biomedical Informatics Research Network (BIRN), we will monitor scanner signal:noise (SNR) monthly with a BIRN phantom, and use as a covariate. Regularized regression techniques will determine which covariates to include in models, e.g., least absolute shrinkage and selection operator (LASSO), with bias correction. These procedures use penalty terms and adjust significance thresholds to allow examination of several variables vs. # participants while minimizing model error and overfitting²⁸⁴. Identified covariates will be tested as potential effects alongside independent variables (IVs; cTBS condition, group).

Hypothesis testing. H1 (Acute cTBS over left vIPFC vs. control and sham conditions on neural measures). Repeated measures analyses of covariance (ANCOVAs), with cTBS condition as a within participant factor, will examine the effect of condition (cTBS over the left vIPFC vs. other conditions) on each primary neural measure change (dependent variables, DVs) in all n=100 participants with useable data on all three scanning sessions, using as covariates cTBS condition order and other covariates as above. Statistical thresholds will be Bonferroni-corrected for 19 parallel ANCOVAs of 19 primary neural change DVs: $p \leq 0.003$. Post-hoc within-group t-tests will determine which specific between cTBS condition neural change measure comparisons are significant for each significant ANCOVA finding, using $p \leq 0.017$ for 3 within group, between cTBS condition post hoc tests.

H2. (Acute cTBS-induced neural change measure-affect change relationships; moderating effect of negative urgency). In order to select the strongest IV predictors for subsequent regression models (below), elastic net penalized regression models (one for each affect rating post cTBS: positive affect, negative affect, Internal State Scale activation, and well-being) will examine in all n=100 participants associations among: **1.** magnitudes of all significant H1 neural measure changes (pre to post cTBS, for each (left vIPFC, left SS, sham) TBS condition relative to each other) from H1 (IVs); and **2.** for left vIPFC and left SS cTBS and sham conditions, acute changes in PANAS positive and negative affect (before each pre TBS scan to after each post TBS scan), and changes in Internal State Scale activation and well-being (post TBS vs. baseline measures) (DVs). There will thus be a

maximum of 12 parallel elastic net models: 3 sets of IVs – all significant neural changes pre to post TBS for a) left vIPFC cTBS; b) left SS cTBS; c) sham TBS (relative to each other); and 4 sets of DVs - the 4 affect change measures above for each TBS condition. (12 within group t-tests will identify the significant affect changes to be used in these models; $p \leq 0.05/12 = 0.004$). The 10 strongest neural measure change IV predictors and covariates for each affect change DV in each of these elastic net models will then be used in each of up to 12 final regression models, to preserve the recommended participant: IV ratio as 10:1. A Bonferroni correction for up to 12 parallel models with 10 IVs each will be used for each model, ie., $p \leq 0.05/(10 \times 12) = 0.0004$. For moderation analyses, regression models will include as IVs and DVs, respectively, neural and affect changes that show significant relationships above, and interactions between cTBS-induced neural changes and negative urgency as additional IVs, using a Bonferroni correction for a maximum of 10 IVs per each of 12 models with $n=100$, as above. Secondary analyses: Regression models will examine relationships between negative urgency and each of 19 baseline neural measures on the first pre cTBS scan per participant; Bonferroni-corrected $p\text{-value} \leq 0.003$; covariates as above. We will examine if negative urgency moderates the effect of cTBS condition on neural measure changes using repeated measures ANCOVAs and variable selection as in H1, focusing on the negative urgency x cTBS condition interaction; statistical thresholds as in H1. Post hoc between-group (median split: high vs. low negative urgency) t-tests ($p \leq 0.05/3 = 0.017$ to control for 1 between-group test for each of 3 post hoc between cTBS condition comparisons) will be performed for each ANCOVA significant interaction.

H3 (BD vs. healthy/ non BD adults). We will examine if group moderates the effect of cTBS-induced neural measure change on affect change, using regression models as in H2, focusing on group x neural measure change interactions; Bonferroni corrected $p \leq 0.0004$, as in H2. Secondary analyses: Similar regression models and thresholds as H2 secondary analyses will compare groups on each of 19 baseline neural measures on the first pre cTBS scan. Similar ANCOVA models and thresholds (and post hoc t-tests) as in H1 will determine if group moderates the effect of cTBS condition on neural changes, focusing on the group x cTBS condition interaction.

Biological variables. H1: repeated measures ANCOVAs IVs: age and gender, age/ gender x cTBS interactions. **H2, H3:** regression model IVs: age and gender, age/gender x cTBS-induced neural measure change interactions.

Exploratory analyses. 1. (cTBS on resting state FC). **2.** (baseline resting state FC, GM, WM, and BD-related response tendency measures as moderators of effects of cTBS on neural-affect change relationships). Methods for examining these neural measures in ROIs/ wholebrain will be as previously. **1.** Repeated measures ANCOVAs as in H1 will be used: extracted resting state FC between left vIPFC and other ROIs/ wholebrain as DVs. **2.** Regression models as in H2 will be used, with interactions between cTBS-induced neural changes and the above pre TBS/baseline neural and BD-related response tendency measures as IVs.

Further exploratory analyses: 1. Associations between: a) hypomanic/ other symptom severity at the beginning of each scanning session and pre cTBS scan RE-related regional and wholebrain activity, FC and resting state FC at each scan session; and b) hypomanic/ other symptom severity at screening and GM and WM structure at baseline structural scan. (In a) and b): height forming $p < 0.001$, $p < 0.05$ FWE clusterwise) in BD and in all adults. Multivariate multiple regression models will be used: symptom severity as IVs, and neural measures, DVs. **2.** Secondary neural measures will be used in all statistical models in H1-H3.

Power (using G Power for H1-H3, and simulation for H2 and H3 moderation effects)

In R21MH108421, we have medium-large effect sizes (ES) for cathodal tDCS over left vIPFC vs. left SS on RE-related left VS activity ($d=0.65$) and left vIPFC-left VS FC ($d=0.78$); and a medium-large ES $r=0.283$ ($d=0.59$) for the relationships between left vIPFC activity during cathodal tDCS over left vIPFC and post scan negative affect. Such ES are likely minimal sizes for results to be of future clinical use. We will, however, use small-medium ES (e.g., $d=0.3-0.67$, $f=0.15-0.25$, $f^2=0.15-0.2$).

H1 ANCOVAs: with $n=100$, $p \leq 0.003$, and a small-medium ES of $f=0.17$, in each ANCOVA model, we will have 80% power to detect a significant effect of cTBS condition in each model.

H1 post hoc t-tests examining significant main effects from these ANCOVAs: with $n=100$, $p \leq 0.017$ and $d=0.33$ for each test, we will have 81% power to detect a significant between cTBS condition contrast.

H2/ H3 regression models, and moderating effect of negative urgency/ group in models: With $n=100$ for neural-affect change relationships, $p \leq 0.0004$, $ES f^2=0.205$, we will have 80% power. (We will have 80% power to detect the specific significant within group changes in affect to be used in these models, with $n=100$, $p \leq 0.004$, $ES=d=0.38$). Simulations using a medium ES and the proposed sampling plan indicate a power of 80.1% to detect significant interactions at $p \leq 0.0004$ between negative urgency/ group and pre-post changes in neural measures on affect changes.

Secondary analyses: H2, H3 regression models for baseline relationships: with $n=100$, $p \leq 0.003$, $f^2=0.155$, and up to 10 IVs in each model, we will have 81% power to detect any significant IV-DV relationship.

H2, H3 ANCOVAs: with $n=100$, $p \leq 0.003$ and a small-medium ES $f=0.17$ in each model, we will have 80% power to detect any significant negative urgency/ BD group x cTBS condition interaction on neural measures.

H2, H3 between-group post hoc t-tests: with $n=100$, $p \leq 0.017$, and $d=0.66$ for each between-group t-test, we will have 81% power.

Exploratory aims: 1. Power for ANCOVAs as in H1; 2. Power for regression models with moderation as in H2.