A Novel Use of a Sleep Intervention to Target the Emotion Regulation Brain Network to Treat Depression and Anxiety

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Statistical Analysis Plan

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Statistical Analysis Plan

Our general approach is to conduct a modified intent-to-treat analysis, in which all available data is included in analyses unless data are artifactual or corrupted. The primary hypothesis in this single-arm phase is that insomnia treatment using CBT-I will be associated with improvements in fronto-limbic brain emotional brain function. Specifically, we predict that sleep restoration will be associated with reduced amygdala reactivity and increased amygdala-mPFC connectivity during emotion fMRI tasks. More specifically, we hypothesize that the reduction in amygdala emotional reactivity will be due to increased top-down regulatory control by interconnected cortical regions. Therefore, the primary analysis plan will be to first examine treatment-associated changes in amygdala reactivity across the three tasks, with FDR correction applied for each task. For tasks and contrasts in which amygdala reactivity is significantly reduced following treatment, we then test whether the reduction in amygdala reactivity corresponds to a parallel increase in connectivity with regions of the mPFC. We aim to test these hypotheses by applying linear mixed-effects (LME) models (R package "lme4"). Random intercepts at the individual participant level will be included in our models to account for the clustering of observations within individuals across time. All statistical models include age and sex as covariates of non-interest.

We also expect to replicate the previously reported improvements in depression and insomnia symptoms following CBT-I. Treatment-related changes in clinical outcomes (depression and sleep) will be tested using LME models with random intercepts. Given the zero-inflation in the measures of suicidal thinking (CSSRS and BSSI), we employ generalized LME models for the negative binomial family to examine treatment-related changes in suicidal thinking.

Additionally, we hypothesize that improvements in fronto-limbic brain function will be associated with parallel improvements in both primary and secondary measures of depression and sleep outcomes. We will test these hypotheses using linear regression with fronto-limbic activation and connectivity change scores (post-treatment minus pre-treatment) as predictors and depression or sleep change scores as outcomes. Diagnostic checks revealed that residuals were not normally distributed for models including changes in suicidal thinking as the outcome (Shapiro-Wilk test, $p < 0.05$). Therefore, we will use a non-parametric bootstrap with 5,000 resamples (R package 'boot') to derive confidence intervals and p-values for each predictor. We report the original OLS coefficients (b), along with 95% bias-corrected and accelerated (BCa) confidence intervals and two-sided p-values derived from the bootstrap distributions.

We will also examine whether changes in objective and subjective insomnia symptoms are related to depression symptom improvements using OLS regression. We expect the degree of depression symptom improvement will be associated with increased sleep efficiency and reduced self-reported insomnia symptoms. Models including BSSI as the depression change outcome will use non-parametric bootstrap to derive confidence intervals and p-values.

Last, we aim to test whether pre-treatment inter-individual differences in fronto-limbic brain activity and connectivity, objective sleep efficiency, and self-reported insomnia symptoms are predictive of the magnitude of depression symptom improvement. We specified residualized change models, which isolate the relationships between pre-treatment inter-individual differences and post-treatment depression symptoms, accounting for baseline depression levels. As above, models including the BSSI employed non-parametric bootstrapping to derive confidence intervals and p-values. We hypothesized that those with greater pre-treatment fronto-limbic dysfunction (higher amygdala reactivity and lower amygdala-mPFC connectivity) and worse insomnia symptoms (lower objective sleep efficiency and higher subjective insomnia symptoms) would experience the greatest improvements in depression symptoms following CBT-I.