Role of Slow-wave Activity and Plasticity in MDD

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Study Protocol

The focus of the project is to assess the impact of slow-wave disruption on plasticity in major depression. Following enrollment, subjects will establish a regularized bed/wake schedule based on their usual bed/wake time monitored in-home by sleep diary and actigraphy for 5 days. All subjects will then spend two nights in the sleep lab – a baseline night and an experimental slow-wave disruption night. On the experimental night, an acoustic tone will be used to decrease slow wave activity (SWA) without waking the subject. The order of nights will be determined via randomization. Between all visits, participants sleep at home on a regular sleep schedule, confirmed by sleep diaries, and actigraphic recordings.

All participants take part in 3 visits to the laboratory:

1. Visit 1: A screening and consenting visit involving informed consent, clinical assessment interviews, self-report measures, and an orientation to TMS and slow-wave disruption procedures.

2. Visit 2: A baseline night in the laboratory where participants spend the night in our sleep laboratory having their sleep monitored, followed by a morning blood draw, and assessment of mood via the clinician-administered Hamilton rating scale for depression, and battery of questionnaires including the Beck Depression Inventory II, two Visual Analogue Scales measuring positive and negative mood, respectively, and Karolinska Sleepiness Scale to assess sleepiness tasks. Additionally, participants will complete a battery of tasks including a resting EEG protocol to assess waking EEG theta power, and two learning and memory tasks, the N-Back, and Paired Associated Learning, followed by the TMS protocol, where motor evoked potentials and intracortical facilitation will be assessed.

3. Visit 3: A slow-wave disruption night where slow-wave activity will be experimentally reduced using acoustic tones administered when sleep technologists detect slow-waves from real-time EEG monitoring, followed by the same procedures as detailed in Visit 2.
Note that the order of baseline night and slow-wave disruption night is counterbalanced, with all participants undergoing both nights.

Statistical Analysis Plan

SPECIFIC AIM 1: Compare multiple, indirect indices of synaptic strength and plasticity in patients with MDD to healthy controls, and to their relationship with SWA. Aim 1 will be achieved by testing null hypotheses that the mean values at baseline are equal between HC and MDD. Hypotheses will be tested using two-sample t-tests with adjustment for multiple outcomes addressed using the methods described above. Regression and correlation analyses will be used to evaluate the degree to which synaptic strength/plasticity variables are associated with SWA. Predictions: (Hypothesis 1.1) The MDD group will demonstrate lower values of synaptic strength (lower total theta power, lower amplitude TMS-evoked potentials) and plasticity (lower levels of serum-derived BDNF, worse performance on behavioral measures of learning and memory) compared to HC at baseline. (Hypothesis 1.2) In those with MDD there will be a positive relationship between measures of synaptic strength and plasticity (total theta power, TMS-evoked potentials, BDNF, performance on behavioral measures) and SWA in the first

NREM period that is not present in HC, such that lower values of synaptic strength and plasticity are predicted for subjects with lower SWA.

SPECIFIC AIM 2: Determine if SWA disruption alters measures of mood, and measures of synaptic strength and plasticity in a sample of individuals with MDD. Regression will be used to model if SWA is directly associated with mood, and synaptic strength/plasticity variables. Predictions: (Hypothesis 2.1) There will be a positive relationship between SWA and negative mood scores (HAM-D, Negative VAS), such that lower SWA will be associated with lower negative mood scores. (Hypothesis 2.2) There will be a positive correlation between reductions in SWA and improvements in synaptic strength/plasticity variables (total theta power, TMS-evoked potentials, BDNF, performance on behavioral measures), such that subjects with the greatest reductions in SWA will are expected to have the largest improvements in synaptic strength/plasticity endpoints. Since the scientific hypothesis is clearly one-sided, one-sided tests of the hypotheses of zero correlation will be performed controlling the type 1 error rate for the set of 5 comparisons using Holm-Bonferroni method described above. Therefore, the first test will be conducted at a 1-sided type 1 error rate of $\alpha=0.01$.

SPECFIC AIM3: Explore if males with MDD are more sensitive to SWA and plasticity-related impairment. The MDD sample will be stratified by sex, resulting in two equal groups, males and females. The analyses described for Aims 1 and 2 will be repeated stratified by sex. Focus will be on descriptive comparisons of sex-specific effect sizes since the study is not powered for within sex comparisons. However, statistical comparisons between sex will be performed and where appropriate 95% confidence intervals for differences between sex in relevant effect sizes will be constructed in order to evaluate the likely ranges of sex-based differences. It is expected that sex differences, if any, are magnified in MDD and may be much smaller in HC. Therefore, if sex differences in HC appear relatively small, the analyses for Aim3 will also compare male MDD and female MDD to all HC. Results from Aim3 will be considered hypothesis generating. Predictions: (Hypothesis 3.1) MDD males will demonstrate lower SWA, and lower values of synaptic strength and plasticity (total theta power, TMS-evoked potentials, BDNF, performance on behavioral measures) compared to MDD females and HC at baseline. (Hypothesis 3.2) Males with MDD will also have larger synaptic strength and plasticity difference score values than females with MDD.