Title: Transcranial Direct Current Stimulation for Pain Treatment in Gulf War Illness

NCT03312920

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Statistical plan:

1. Study Overview and Objectives

The study evaluates the efficacy of transcranial Direct Current Stimulation (tDCS) for managing pain in Gulf War Illness (GWI) veterans. The specific objectives are to determine if tDCS targeting the occipital nerve reduces pain and to identify EEG and rsfMRI-based markers that correlate with pain relief.

2. Study Design and Groups

- **Design**: Prospective, double-blind, randomized controlled trial with a parallel-group design. This prevents potential carry-over effects from sham to treatment phases.
- **Groups**:
    - **Active tDCS Group**: Real tDCS targeting the occipital nerve at 1.5mA for 20 minutes.
    - **Sham tDCS Group**: Sham tDCS with a brief current sensation to maintain blinding but no sustained current.

3. Sample Size and Power

- **Primary Outcome**: Pain severity on the Visual Analogue Scale (VAS).
- **Secondary Outcomes**: Questionnaire measures (MFIS, PSQI, BDI, PCS, MGPQ, PVAQ) and neurophysiological measures (LEP, EEG, rsfMRI).
- **Sample Size**: 60 participants (30 per group), allowing an 80% power to detect a 1.1 cm difference on the VAS scale (Cohen's d effect size) with a significance level of 0.05. The design anticipates a 10% dropout rate.

4. Data Collection Timeline

- **Assessment Points**:
    - **Baseline**: Pre-treatment assessment.
    - **Immediate Post-Treatment**: After the 10 tDCS sessions.
    - **Follow-Up**: 4 weeks, 12 weeks, and 24 weeks post-treatment.

5. Data Management

- **De-identification and Confidentiality**: Data will be stored under a de-identified code compliant with HIPAA regulations and protected by a Certificate of Confidentiality. Only authorized personnel will access the data.
- **Data Storage and Disposal**: Data will be stored securely and deleted seven years post-study completion.

6. Statistical Analysis Plan

A. Primary Outcome Analysis: Pain Severity (VAS)

- **Modeling**: Mixed-effects repeated-measures ANOVA with group (treatment vs. sham) as a between-subjects factor and time (baseline, immediate post-treatment, 4-week, 12-week, 24-week) as a within-subjects factor.
- **Post-Hoc Tests**: Bonferroni-adjusted post-hoc tests will examine specific time points if interaction effects are significant.
- **Intention-to-Treat (ITT) and Per-Protocol Analyses**:
    - **ITT**: Last observation carried forward (LOCF) for missing data.
    - **Per-Protocol**: Include only participants with at least 8 out of 10 therapy sessions completed and no interfering medications.

B. Secondary Outcome Analysis

- **Questionnaires**: MFIS, PSQI, BDI, PCS, MGPQ, and PVAQ will be assessed using repeated-measures ANOVA to evaluate time × group interactions.
- **Neurophysiological Markers**:
    - **LEP**: N2P2 amplitude and latency will be assessed using repeated-measures ANOVA to evaluate group (treatment vs. sham) × time (baseline vs. immediate post-treatment) interactions. Correlations between VAS changes and N2P2 amplitude differences will be analyzed with Pearson correlations.
    - **EEG**: sLORETA contrast maps will analyze voxel-by-voxel comparisons (pre- vs. post-tDCS) to determine active vs. sham differences. Randomized statistical thresholding (5000 permutations) will correct for multiple comparisons.
    - **rsfMRI**: Seed-based functional connectivity analyses will target key regions (dACC, pgACC, amygdala, and insula). Group-level comparisons (treatment vs. sham) will assess changes from baseline to post-treatment and correlate with VAS scores to evaluate pain reduction prediction.

7. Exploratory Analysis

- **Correlation Analyses**: Correlate rsfMRI connectivity changes and EEG contrast map changes with VAS pain reduction to identify neurophysiological predictors of pain relief.

8. Blinding Integrity and Control Measures

- Post-treatment, participants will guess their treatment group to assess blinding effectiveness. Medication changes will be monitored to ensure consistency.

9. Handling Missing Data and Sensitivity Analysis

- **Imputation**: Apply multiple imputation if the missing rate is above 10%.
- **Sensitivity Analysis**: Compare results with and without LOCF to ensure robust findings.

This statistical plan aligns with the study objectives and incorporates the additional neurophysiological and data management details.

Deviation statistical plan:

The study was unfortunately disrupted due to the impact of COVID-19, which led to its discontinuation. Consequently, we have been limited in our ability to collect and analyze comprehensive data, and are currently only able to report descriptive statistics. We acknowledge that this is a limitation in our findings, and we are exploring potential avenues to resume the study and gather more robust data in the future.