Enhancing Acupuncture Treatment Effect Through Non-invasive Neuromodulation

NCT number: NCT03716830

Date: 12/1/2023

Study Protocol and Statistical Analysis Plan

Study protocol

We conducted a randomized clinical study at Massachusetts General Hospital (MGH), enrolling chronic low back pain patients and assessing the clinical and brain imaging outcome measures. The study involved treatment with real or sham acupuncture and real or sham tDCS using a 2 x 2 design.

Participants

Participants enrolled in the study were included if they had been experiencing chronic low back pain and had at least 4/10 clinical pain on the 11-point Low Back Pain Numeric Rating Scale (LBP-NRS). More details are presented in the supplementary material.

Randomization

Participants were randomized to four groups: real acupuncture plus real tDCS, real acupuncture plus sham tDCS, sham acupuncture plus real tDCS, and sham acupuncture plus sham tDCS. VGAIT-LBP study: Participants were randomized to either the AB-VGAIT or the AB-VGITT group. The randomization, designed by a biostatistician, was maintained with all keys secured in an excel file.

Blinding/Masking

In both studies, the principal investigator, outcome evaluators, and statisticians were blinded to the group assignments. Also, both tDCS and acupuncture assignments were blind to participants, though acupuncturists were not.

Intervention

Real acupuncture plus real tDCS group: Participants received acupuncture (about 30 minutes) at Yaoyangguan (GV3), bilateral Shenshu (BL23), Weizhong (BL40) and Taixi (KI3), and 1-3 Ashi acupoints based on palpatory tenderness[22,23] (Figure 1). Concurrently, real tDCS was applied for 20 minutes to bilateral primary motor cortices (see supplement for details).

Real acupuncture plus sham tDCS group: The acupuncture procedure was identical to the real acupuncture plus real tDCS group. For sham tDCS, current was applied for 15 seconds at the beginning and end of the 20-minute session to mimic real tDCS stimulation.

Sham acupuncture plus real tDCS group: Sham acupuncture used validated Streitberger non-penetrating needles[24] placed on non-acupoints (Figure 1), mimicking the same

manipulation of real acupuncture. The real tDCS procedure was administered as described above.

Sham acupuncture plus sham tDCS group:Both sham acupuncture and sham tDCS procedures followed the same protocols as described in their respective combinations above.

The total treatment period was four weeks, with two sessions per week for the first two weeks and one session per week for the last two weeks. Participants reported their sensations using the MGH acupuncture sensation scale (MASS) after the treatment.

Statistical plan

General plan: For all outcomes in this proposal, we will (1) compare resting state functional connectivity (rsFC), cerebral blood flow (CBF), and clinical assessment differences within each group using paired t-tests, and between treatment groups using Analysis of Covariance (ANCOVA); and (2) apply multiple regression analyses to examine the relationships between changes in rsFC/CBF and corresponding clinical outcomes. Additional variables, such as age and gender will be included as covariates to reduce subject heterogeneity.

Resting state functional connectivity analysis

Seed based functional connectivity analysis Seed based rsFC will be applied with CONN toolbox implemented in MATLAB. The pre-processing of fMRI data will include slice-timing correction, realignment, co-registration to subjects' respective structural images, normalization of images to the standard Montreal Neurological Institute template, and smoothing with a 6 mm full width at half maximum (FWHM) kernel. In addition to these steps, we will employ segmentation of gray matter, white matter, and cerebrospinal fluid (CSF) areas for the removal of temporal confounding factors (white matter and CSF). Band-pass filtering will be performed with a frequency window of 0.008-0.09Hz.

To eliminate head motion and artifacts, we will identify outlier time points in the motion parameters and global signal intensity using ART. For each subject, we will treat images (time points) as outliers if composite movement from a preceding image exceeds 0.5 mm, or if the global mean intensity is greater than 3 standard deviations from the mean image intensity for the entire resting state scan.

In addition, 6 rigid body motion parameters, as well as white matter and cerebrospinal fluid (CSF) signals will be regressed out, and images will be normalized using structural image unified segmentation and then re-sampled to 2-mm cubic voxels. After linear de-trending, data will be filtered using a temporal band pass (0.01-0.08 Hz) to remove low frequency

noise and influences of higher frequencies reflecting cardiac and respiratory signals, and finally smoothed using a full width half maximum of 6 mm.

In this study, we will use several seed regions. The first seed region is the bilateral PAG (spheres with 2 mm radius on left and right side, peaks of MNI coordinates ± 4 -26 -14). It will allow us to elucidate the involvement of the descending pain modulation system. The second seed region will be bilateral M1. The reason we chose this location is based on 1) a previous study, where we found this area to show significant differences in functional connectivity between cLBP patients and healthy controls and 2) its proximity to the center of the tDCS location in this study.

Then, the averaged time course will be obtained from the seeds and correlation analysis will be performed in a voxel-wise way to generate the functional connectivity map. The correlation coefficient map will be converted into a Fisher-Z map using Fisher's r-to-z transformation to improve the normality.

Group analysis will be applied using the random effects model. A full factorial design module in SPM12 will be applied with four treatments and two time points (before and after treatments). Specifically, we will compare the pre- and post-treatment PAG rsFC (and the control seed) and M1 rsFC differences across different treatments. ACOVA analyses will be applied between PAG rsFC changes (pre- minus post-treatment) and the corresponding clinical assessments and QST changes respectively. A threshold of $p < 0.005$ and $p < 0.05$ small volume corrected will be applied for the regions of interest (ROIs). A threshold of $p < 0.005$ uncorrected and $p < 0.05$ Family-wise Error (FWE) corrected threshold will be used for non-ROIs. The ROIs include: ACC, MPFC, MCC, insula, S2, DLPFC, and parietal lobule.

ASL data analysis

ASL data will be collected before and after the first and last treatments. Data analysis will be applied using a method applied in our previous studies. The pre-statistical processing for each subject will include head motion correction, skull stripping using FSL's Brain Extraction Tool (BET), smoothing with a Gaussian 5 mm FWHM filter to reduce spatial variability, and a 100 s high-pass temporal filtering. In order to quantify perfusion (CBF), even and odd images will be subtracted (60 pairs) and averaged to produce an average CBF-weighted image. Quantification of perfusion will then be performed using a single compartment model that assumes a well-mixed single compartment model. Group analysis will be applied using ANOVA. The same threshold used for the rsFC data analysis mentioned above, will be applied.