PROTOCOL TITLE

Neuromodulation of placebo and nocebo effects

IDENTIFIER

NCT03102710

DATE

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BIOSTATISTICAL ANALYSIS

Specific Aim 1: Characterize the neural mechanisms by which tDCS to rDLPFC modulates placebo / nocebo responses in healthy subjects in an acute pain paradigm.

Primary outcome: 1) fMRI signal changes evoked by identical experimental pain in different conditions (before and after different inert creams) after different tDCS interventions; 2) placebo and nocebo effect difference (as indicated by pain rating differences) after different tDCS interventions.

Similar to our previous studies [1-3], fMRI data processing and statistical analyses will be carried out using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing will include co-registration, motion correction, normalization to MNI stereotactic space, and spatial smoothing with an 8 mm Gaussian kernel. Then, for each subject, the nine contrasts (placebo, nocebo and control condition by pain anticipation, pain administration and pain rating) with the fixation (baseline) will each be calculated using a general linear model.

Group analysis will be performed using a random-effects model. A full factorial module in SPM 8 will be performed to test the differences between the inert Lidocaine, Capsaicin and control creams during pain anticipation, application and intensity ratings separately within each group; then we will compare the differences (between the Lidocaine and control, and Capsaicin and control) among the three groups (tDCS inhibition, tDCS enhancement and sham tDCS) to investigate how tDCS can modulate the placebo and nocebo effects. Covariates including LOT, ERS, STAI scores, gender, and experimenter effect will also be included in the model.

In addition, a multiple regression analysis will be performed between the placebo and nocebo effects as indicated by subjective pain rating differences and corresponding fMRI signal differences by pooling the data of all three groups (group indicator will be included in the model as a covariate). Covariates will include LOT, ERS, STAI scores, gender, and experimenter effect. As in previous studies [2, 4-6], a threshold of voxel-wise $p < 0.005$ with 20 contiguous voxels will be used for pre-defined ROIs. For non-ROI, a threshold of voxel-wise $p < 0.005$ and cluster level $p < 0.05$ Family-wise Error (FWE) corrected will be used.

Specific Aim 2: Characterize the neural mechanisms by which tDCS to rDLPFC modulates functional connectivity of the rDLPFC

Primary outcome: rDLPFC functional connectivity changes before and after different tDCS intervention

Seed based functional connectivity analysis Seed based FC will be applied with a method used in our previous studies [3, 7-10]. In summary, the fMRI data will be preprocessed using Data Processing Assistant for Resting-State fMRI (DPARSF) software [11, 12]. The preprocessing will include slice timing correction, head-motion correction, spatial registration to respective structural images for each subject, 6 rigid body motion, white matter and cerebrospinal fluid signals will be regressed out. After linear de-trending, data will be filtered using a temporal bandpass (0.01-0.08 Hz), and finally smoothed using a full width half maximum of 6 mm. FC analysis for individual subjects will be carried out in DPARSF by applying the seed-based approach. In this study, we will use rDLPFC [13, 14] as seed.

Group analysis will be performed using the random effect model with SPM8. A full factorial model module in SPM8 will be applied: three groups (excitability enhancement, inhibition and sham), two tDCS (first and third) with two conditions (pre and post-treatment). To investigate the incremental effect across the first and last tDCS, we will compare pre- and post-treatment differences in tDCS 1 and 3 of each group. To investigate the incremental effect across three time points, we will also apply the same analysis on the pre-tDCS rsFC in tDCS 1 and 3. In addition, a multiple regression analysis will be performed between the placebo and nocebo effects (indicated by subjective pain rating differences between Lidocaine / Capsaicin and the control condition) and rsFC after the third tDCS by pooling the data of all three groups (group indicator will be included in the model as a covariate). LOT, ERS, STAI scores, gender, and experimenter effect will also be included as covariates in the analysis. A threshold of $p < 0.005$ will be applied for the region of interest. A threshold of $p < 0.001$ uncorrected and $p < 0.05$ corrected will be used for non-ROI brain areas.

Reference

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