PROTOCOL TITLE

Neuromodulation of placebo and nocebo effects

IDENTIFIER

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SPECIFIC AIMS

Specific Aim 1: Characterize the effect of applying tDCS to the rDLPFC to modulate placebo and nocebo effects in healthy subjects

Hypothesis 1.1: In the sham tDCS group, placebo lidocaine and capsaicin will produce a significant pain rating decrease (placebo) and increase (nocebo) respectively, in response to identical heat pain stimuli as compared to a within-subject control "neutral" cream. Both effects will be augmented by tDCS enhancement of rDLPFC excitability and blunted by tDCS inhibition of rDLPFC excitability.

Hypothesis 1.2 In the sham tDCS group, placebo treatment will produce fMRI signal increases in regions associated with the DPMS including the DLPFC, orbital prefrontal cortex (OPFC), rostral anterior cingulate cortex (rACC), periaqueductal gray (PAG), and fMRI signal decreases in pain intensity sensitive regions (insula and secondary somatosensory cortex, S2), as compared to the within-subject control in response to identical pain stimuli. These changes will increase in the tDCS enhancement cohort and blunt in the inhibition cohort.

Hypothesis 1.3 In the sham tDCS group, nocebo treatment will produce fMRI signal increases in brain regions associated with cognition and anxiety, including DLPFC, hippocampus, and OPFC, along with fMRI signal decreases in the areas associated with the affective component of pain (dorsal anterior cingulated cortex (dACC) and insula), as compared to the within-subject control neutral cream. These fMRI signal changes will be blunted in the tDCS inhibition group and increased in the tDCS enhancement group.

Specific Aim 2: Characterize how tDCS to rDLPFC can modulate functional connectivity of rDLPFC

Hypothesis 2: Enhancing rDLPFC excitability will increase resting state functional connectivity (rsFC) between the rDLPFC and rACC and insula whereas inhibiting rDLPFC excitability will decrease rsFC between the rDLPFC and rACC and insula as compared with sham tDCS. The rsFC between rDLPFC and rACC will be associated with placebo effect as indicated by pain rating difference.

STUDY PROCEDURES

We will recruit healthy subjects for this study. Please see the Protection of Human Subjects section for detailed entry criteria for screening and recruitment. In this experiment, subjects will be randomly assigned to three groups (26 per group): 1) tDCS enhancement group to increase the excitability of rDLPFC, 2) tDCS inhibition group to decrease the excitability of rDLPFC, and 3) sham tDCS group.

Subjects will participate in five experimental sessions: a training and familiarity session, contextual learning/expectancy boost session, two tDCS sessions, and a session combining tDCS and testing for placebo/nocebo effects. Sessions 1and 2 will be separated by 2-5 days, sessions 2 and 3 will be separated by 1-5 days, then sessions 3, 4, and 5 will be applied on consecutive three days. We will measure tDCS effects via changes in subjective pain ratings, fMRI signals in response to calibrated heat pain and the rsFC.

Detailed experimental procedure

Noxious heat stimuli will be delivered using a PATHWAY system (Medoc Advanced Medical Systems). All stimuli will be initiated from a baseline temperature of 32 °C and increased to a target temperature. Each stimulus will be presented for 12 seconds, including 2.5 seconds to ramp up to the target temperature and 2.5 seconds to ramp down to baseline again. Heat stimuli will be applied to the right volar forearm**. In sessions where tdcs is applied we will administer the tdcs sensation questionnaire to ensure subjects did not have any unexpected adverse reactions.**

Randomization Subjects will be randomized into one of three groups using a centrally generated variable-sized block design: tDCS enhancement, tDCS inhibition, and sham tDCS groups.

Session 1 is a training, familiarity, and calibration session. Subjects will be trained to use the Sensory Gracely Scale (0-20) [1, 2] to rate pain experiences using the same method as in our previous studies [3, 4]. Subjects will first receive an ascending heat stimulus sequence (starting from 38 degrees). The three temperatures that each subject rates as approximately 5-6 (mild pain), 10-11(moderate pain) and 14-15 (strong pain) will be selected. Subjects will receive a urine drug test on this day to determine no substance abuse.

Session 2 is an expectancy manipulation session [3-5]. At the beginning of the session, all subjects will be informed that the aim of this study is to use a neuromodulation tool (tDCS) to investigate the analgesic effects of lidocaine cream and the hyperalgesic effects of capsaicin cream using a neutral cream as a control. We will first apply sham tDCS for 20 minutes, and then apply all 3 creams to different spots on participants' right volar forearm. Subjects will be told that the creams will need about 20 minutes to take effect and that the effect will last for more than two hours. *In reality*, only sham tDCS will be applied, and an inert cream will be used for all 3

creams. The cream will be a fragrance-free moisturizing lotion dyed three different colors (blue for "Lidocaine," pink for "Capsaicin," and white for neutral).

After this scripted explanation, 9 unique regions of the subject's arm will be demarcated for each stimulus. We will draw a 3x3 grid comprised of 2 cm x 2 cm squares on the subject's right volar forearm, starting the grid at the subject's elbow crease. (If the volar portion of the arm is not wide enough to accommodate the 6 cm width required, we will draw one 1x3 column on the radial, lateral portion of the forearm.) The creams will then be applied with each cream spread onto a unique set of 3 adjacent squares (i.e. one cream for each row). The row placement of the neutral control cream, placebo Lidocaine and Capsaicin creams will be randomized between subjects.

Using methods similar to those of previous studies [5, 6], subjects will then be told that to test the hyperalgesia effect of capsaicin and the analgesia effect of the lidocaine, 6 identical pain stimuli will be applied to each of the nine spots. However, in reality, to boost subjects' expectancy, 6 *moderate* stimuli will be given to each of the neutral control cream spots, 6 *mild* stimuli will be applied on placebo Lidocaine cream spots, and 6 *high* stimuli will be applied on nocebo Capsaicin cream spots**.** The location of the placebo, nocebo and control rows will be randomized across subjects to balance the experimental design. Subjects will be asked to rate their expectancy of both the analgesic effect of lidocaine cream and the hyperalgesic effect of capsaicin using a 0-10 scale (with 0 indicating a very negative expectation of "does not work at all" and 10 indicating a very positive expectation of "very effective") before the pain stimulus is applied and again how much they expected the cream reduced or enhanced their pain afterward. The Gracely Sensory and Affective Scale will be used to rate experienced pain during the stimulation afterward.

Session 3 is the first tDCS session. Right before and after tDCS, resting state fMRI data will be collected.

Session 4 is the second tDCS session with no fMRI scan involved.

Session 5 is the third tDCS and placebo / nocebo test session. At the beginning of the Session, subjects will be told that the Session 2 procedure will be repeated in the fMRI scanner. As in Session 2, the 3 different creams (in reality all one inert cream) will be administered to each row of squares, with "lidocaine" and "capsaicin" cream administered to the same rows as determined in Session 2. Then, tDCS will be applied based on subjects' randomization. The resting state fMRI data will be collected before and after tDCS.

After that, calibrated pain will be applied during the fMRI scan. Since this session will test the placebo/nocebo effect, we will only administer different heat stimuli to the 3 regions in the most lateral column of the 9 x 9 grid. Then, subjects will be asked to rate their expectancy of both the analgesia effect of lidocaine cream and the hyperalgesic effect of capsaicin using a 0-10 scale. After that, we will administer the same moderate stimulus to all remaining regions with all 3 creams. Our outcome measurement will be the subjective pain ratings and fMRI signal changes to identical calibrated heat pain.

At the end of the experiment, subjects will be debriefed by a licensed physician or by the Principal Investigator, Jian Kong. We will inform them that in this study, only inert cream and sham tDCS (in session 2 or in sham tDCS group) was used, and that we changed the heat pain temperature at session 2. We will also emphasize that the experience of this study should not influence their impression of lidocaine / capsaicin or their interest in choosing these drugs as a potential therapeutic method.

Transcranial direct current stimulation (tDCS) administration

Twenty minutes of tDCS at 2mA will be applied by the StarStim system. For the rDLPFC excitability inhibition group, the cathodal electrode will be placed over F4 and the anodal electrode above the left orbit. For the rDLPFC excitability enhancement group, the anodal electrode will be placed over F4 and the cathodal electrode above the left orbit. Stimulation will start and finish with a 15 second gradual current ramp up and ramp down to decrease subjects' discomfort. For sham tDCS treatment, stimulation will be applied only at ramp periods at the beginning and end of sham stimulation to mimic the somatosensory effect of real tDCS for 15 s. As in a previous study [7], the electrodes will be placed at the same positions for the real tDCS (half rDLPFC enhancement position, half rDLPFC inhibition position).

fMRI data acquisition

The MRI scan will be performed using a 3 Tesla Siemens MRI System equipped for Echo Planar Imaging using a 32 channel head coil. fMRI data will be acquired using gradient echo T2*-weighted sequence (TR/TE=2000/30 msec, flip angle=90º, slice thickness=3 mm). The scans will include pre-tDCS resting state (8 minutes) and post-tDCS resting state (8 minutes) scans during the application of heat pain stimuli to different spots. For pain stimuli at each spot, a paradigm used in our previous study [8] will be applied, which include

anticipation, pain and pain rating, each pain sequence at one spot lasts about 5 minutes (**Figure 6**). A high-resolution 3D MPRAGE sequence with 1 mm^3 isotropic resolution will also be collected for anatomic localization of the fMRI signal changes. tDCS (20 minutes) will be applied in the scanner as our tDCS device is MRI compatible.

Reference

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