Title of Study: Modulation of Spontaneous Cortical Activity by tDCS: BRAIN Initiative I

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Study Protocol

Transcranial direct-current stimulation (tDCS) is a form of noninvasive brain stimulation that uses small metal electrodes placed on the scalp to deliver a constant, low-amplitude current to brain areas of interest. This current is thought to increase or decrease local neuronal excitability, depending on the brain area and type of stimulation. Anodal stimulation is generally thought to cause neuronal resting-membrane depolarization and decreased local GABA, which in turn increases neuronal excitability and promotes neuronal firing. Cathodal stimulation, on the other hand, is generally thought to cause resting-membrane hyperpolarization and decreased local glutamate, which decreases neuronal excitability and suppresses neural firing. However, these effects have generally been studied in only model systems and the neural effects in the human neocortex are poorly understood. The current study aims to address this gap in knowledge by combining tDCS with a new dynamic neuroimaging method known as magnetoencephalography (MEG). MEG is noninvasive and provides highly accurate measures of ongoing neurophysiology. These measures include spontaneous neural activity, which reflects the background rate of neuronal firing in the absence of endogenous and exogeneous input (i.e., the seemingly random discharges that human cortical neurons exhibit), as well as oscillatory activity which reflects information processing among large groups of neurons. Typically, both spontaneous and oscillatory neural activity is divided into frequency bands of activity (e.g., alpha, gamma) and these different bands are thought to roughly correspond to different circuits and/or different cognitive processes. Thus, in this study investigators will evaluate the impact of different types of tDCS on behavior and spontaneous and oscillatory neural activity in healthy adults. Investigators will use a cross-over design where all participants complete all stimulation conditions (i.e., anodal, cathodal, and sham) and will focus on behavioral performance, in terms of accuracy and reaction time, and alpha and gamma frequency neural activity because these two bands have been shown to be critical to visual processing.

Each participant will complete a total of four visits, with each visit being separated by at least one week. The effects of tDCS are thought to last only a few hours so the one-week wash-out period should be more than adequate. During Visit 1, participants will complete cognitive and psychiatric screens and a structural MRI session. This high-resolution structural MRI is needed for tDCS electrode placement using our navigational system and for current flow modeling to derive the optimal placement of electrodes for maximum stimulation of targets. Prior to Visit 2, each participant will be randomized to the sham, anode, or cathode-first group, which will determine the stimulation montage for each of their subsequent visits. Note that all participants will complete each condition (anode, cathode, and sham) during a separate visit. During Visits 2-4, each participant will undergo 20 minutes of high-definition tDCS during a passive visual stimulation paradigm, and then be moved to the MEG chamber for neural recording. During each MEG session, participants will complete measures of perceptual processing. The outcome measures include behavioral changes (i.e., reaction time and accuracy) and neuronal changes (i.e., spontaneous alpha and gamma activity, oscillatory alpha and gamma activity) induced by the different types of stimulation relative to sham.

Statistical Design & Power

Sample Size Considerations: Included are estimates of attrition, MEG success rates based on our prior imaging experiences, and measures of effect size based on the results of our preliminary studies in calculating our necessary sample size. To estimate the effect size, investigators computed Cohen's d using data from a perceptual processing task where participants were assigned to a single stimulation type. Investigators focused on the average effect size for stimulation group differences, which was d = 0.96. This suggests that 34 participants per group (anode, cathode, sham) would be adequate to detect differences at 0.01 alpha with 0.90 power. Note that the design of the current study is a cross-over type where each participant will complete all three stimulation conditions in a random order. All things being equal, it would be expected that the effect sizes to be larger in the proposed studies due to the within-subjects design (i.e., the preliminary data used to calculate effect sizes followed a between-subjects design). However, this is not necessarily the case and investigators should be powered to examine sex differences in the impact of tDCS on spontaneous and oscillatory neural activity in future work. Thus, the aim is 124 complete data sets, but it is anticipated that enrollment up to 150 participants to reach this number may be needed, as the multiple visits could lead to larger attrition than we have observed in our pilot studies, and MEG technical difficulties on 3-5% of participants are expected.

Primary Statistical Analyses: The behavioral data analyses will involve computing the accuracy rate for each participant (i.e., the percentage of trials where the participant responded correctly) and the mean reaction time. The reaction time reflects how quickly the participant responded to the visual stimuli presented during the MEG and will be the average of all correct trials during the perceptual processing task, which consists of 240 total

trials. Once these metrics are computed per person, investigators will compute mean accuracy and reaction time for each stimulation condition, which will be the outcome metrics. Faster rection times and higher accuracy reflect more favorable outcomes following the particular type of stimulation relative to sham and can be assessed using an ANOVA per measure with follow-up post-hoc testing to identify the specific direction of any significant effects. As per the MEG, the raw data will transformed into the time-frequency domain and imaged, per participant, frequency band (alpha, gamma), and condition, using an advanced beamforming approach. The resulting images are comprised of neural response amplitude values in each of thousands of voxels (i.e., cubes of tissue). Investigators will then compare the amplitude of each voxel for stimulation effects using a whole-brain mass univariate approach in the Statistical Parametric Mapping (SPM12) software. The resulting statistical F- maps of neural oscillatory activity will reveal brain areas with significant differences by stimulation condition, and then use post-hoc testing will be used to derive the direction of the effect. In addition, investigators will extract the time series from these significant clusters by computing a virtual sensor at the peak voxel. These time series will enable us to compute the spontaneous activity level during the baseline period and this will be used to determine whether there are differences in spontaneous neural activity by stimulation condition. For these analyses, separate ANOVAs will be computed for each cluster. Note that all statistical analyses will be done separately for the alpha and gamma maps and multiple comparisons correction will use the Bonferroni method.