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Brief Title:	Auditory Control Enhancement (ACE) in Schizophrenia (ACES)
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Study Protocol

Objectives

Although Auditory Control Enhancement (ACE) shows promise for treating AH, evidence for neural target engagement is needed to move forward with efficacy trials. In alignment with NIMH priorities, we plan to incorporate objective measures that test the delivered dosage and the proposed mechanism of action of the intervention and determine if the intervention target has been modulated. MRI and EEG afford parametric tests of biophysical and neurophysiological target engagement. In the proposed research, we will investigate biological target engagement in two sham-controlled experiments. In this study, we will determine whether tDCS of the auditory control network (rVLPFC anode and left TPJ cathode) leads to alterations in electric field and blood oxygenation level dependent (BOLD) response in the auditory control network during stimulation using Dual-Echo Echo Planar Imaging. Additionally, we will examine the degree to which ACE modifies behavioral and neurophysiological markers of cognitive control.

Design

Participants were randomly assigned to either active/verum or sham/placebo tDCS in a parallel-arm, 2x2 between-subjects repeated-measures design.

Methods

Prior to obtaining informed consent, participants underwent a telephone screening using a standardized script, which took approximately 15 minutes. After consent was obtained, a hearing test using the method of ascending limits (Grayson-Stadler GSI 17 Audiometer) was administered by Dr. Coffman or trained research staff to rule out hearing loss, as this was essential for the auditory sensation experiment. This test was conducted in the research offices at Western Psychiatric Hospital and lasted about 15 to 30 minutes during the first session. Participants who did not pass the hearing test were advised to contact their primary care provider. Additionally, participants completed the Society of Magnetic Resonance Imaging's standardized MRI screening protocol prior to each MRI visit, which took about 10 minutes.

Demographic and medical history information was collected using a standard form during the first visit. Clinical and diagnostic assessments included the Structured Clinical Interview for DSM Disorders (SCID), which lasted approximately 1.5 to 2 hours. Additional assessments included the Positive and Negative Syndrome Scale (PANSS), Psychotic Symptoms Rating Scales (PSYRATS), and Global Functioning: Social and Role Scales.

These assessments collectively took about two hours, with PSYRATS administered both before and after ACE.

Neuropsychological testing involved the full MATRICS battery, targeting six cognitive domains affected in schizophrenia, and subtests from the WASI to assess general intelligence. The MATRICS battery took about one hour, and the WASI took approximately 30 minutes. Both were administered before and after ACE.

During the Auditory Control Enhancement (ACE) procedure, participants received transcranial direct current stimulation (tDCS) while performing a simple cognitive task. They were randomly assigned to receive either full-duration tDCS or a 30-second version (sham). Dr. Coffman randomized participants based on their order of entry into the study. The study was single-blind, with participants unaware of their group assignment. Electrodes were placed over the right ventrolateral prefrontal cortex (anode; F8) and the left temporoparietal junction (cathode; CP5). tDCS sessions, conducted at WPH (Thomas Detre Hall and Oxford), were administered by Dr. Coffman or trained staff. The current strength was set to 2.0 mA and was delivered for 30 minutes per session using saline-soaked sponge electrodes (10 cm^2 in size). Stimulation began two minutes before the task to assess discomfort, and skin sensation was checked verbally at least twice during stimulation. Participants were reminded they could withdraw at any time, and electrodes were never placed over the heart, eyes, or ears.

During tDCS, participants performed a cognitive task designed to train attention, working memory, and processing speed, lasting about one hour. The first ACE session involved a circular image with a single radius line, resembling a clock hand. Participants held a button to start each trial and released it when the line reached a target point. The task increased in difficulty by removing visual cues. ACE sessions 2 and 3 utilized simple button-response tasks and assessed reaction time and time estimation, respectively, using only basic shapes and lines.

EEG testing was led by Dr. Coffman with support staff utilizing a 32-channel Starstim system. EEG amplifier bandpass was open (DC) to 166 Hz (24 dB/octave rolloff) digitized at 500 Hz. ASSR and AX-CPT stimuli were be presented using Presentation software (NeuroBehavioral Systems). Timings of stimuli were confirmed by oscilloscope, and loudness confirmed with a sound meter and artificial ear canal. Sounds were created with NCH Tone Generator and edited in NCH Wavepad (NCH, Australia) and were presented over Etymotic 3A insert earphones. We measured differential 40Hz ASSR gamma power between attend/ignore conditions and beta-band oscillatory power in the AX-CPT as neurophysiological measures of auditory control network function. **ASSR.** Biphasic click trains were presented at 40 Hz (80 db, 500 ms duration, 1000 ms ±200 ms ISI). Subjects

once ignored the click trains and watch a silent video, and once listened to the clicks, pressing a button to click train presented at reduced intensity (75 db, 10% of trials) . We recorded 360 trials each under attend/ignore conditions. We assessed 35-45 Hz gamma power in frontocentral electrodes in attend and ignore conditions, as well as the difference between attend/ignore measurements. **AX-CPT** uses a combination of Latin letters as cues and probes following the established A-then-X rule. More specifically, the rule for the AX- is that 'X'' is the target when directly preceded by the letter "A'' trials, whereas a letter in any other sequence is a nontarget (e.g., AY, BX, and BY trials, where a B is any non-A cue, and a Y is any non-X probe). The AX and BX trials both require the representation and maintenance of the cue, or the goal of the task, to respond appropriately. BX trials tend to be the most sensitive to impairments in the ability to maintain the goal representation. That is, maintenance of the B cue is required to overcome the prepotent target response to the X on the trials when it does not follow an A. The most difficult trial is AY, given that goal focused maintenance of the A cue should produce a high expectancy of a subsequent X probe and preparation of a target response, resulting in increased errors or slowing on AY trials. 450 trials were presented in 6 blocks of 75 trials. The cue was presented for 500 ms with ISI of 1000 ms. Cognitive control was indexed by prefrontal beta-band activity following attention-alerting "B" trials. EEG was conducted both before and after ACE.

MRI data were collected using a 3T Siemens Prisma MRI system. Each participant underwent two 13-minute DE-EPI scans to map current flow during tDCS, along with T1 and T2-weighted structural imaging. MRI sessions lasted about one hour and were conducted before and after ACE. Participants completed pre- and post-scan questionnaires to evaluate their scanning experience. Those who reported smoking or consuming coffee within two hours of testing were asked to reschedule if the session could not be delayed.

Participants were asked to rate acceptability on a visual analogue scale, and to guess whether they received active or sham stimulation, using a forced choice questionnaire.