Study Protocol & Statistical Analysis Plan

Title: Enhancing Cognitive Control in Mild Cognitive Impairment Via Non-invasive Brain Stimulation

NCT#: NCT04647032

Last Updated: 11/2/2021

Study Procedures

This study was preregistered at ClinicalTrials.gov with identifier NCT04647032. In this study, participants first met with researchers at the University of California, San Francisco and provided informed consent. Participants received two iPad tablets, one for tACS days and one for outcome measures days. Participants were instructed on the use of each device (with a brief demonstration in front of a mirror with the tACS patches), the timeline of events, and provided with detailed written instructions. Once home and with active internet, participants first completed the outcome measure tasks without any neurostimulation (baseline). On the following day, participants self-applied the neurostimulation device and then completed 20-minutes of adaptive CCT. Participants completed the paired tACS+CCT task in the same manner for the following four days, totaling five consecutive days. On the following (6^{th}) day, participants completed the same outcome measures as baseline without any concurrent tACS (1-week assessment). The next day, one week from the initial session, participants completed the adaptive CCT task with paired tACS again. Participants then had two additional weekly sessions of tACS+CCT. Finally, on the day after the last (8^{th}) tACS session, participants completed a final tACS-free outcome measures session (1-month assessment).

Participants

In this double-blind parallel-group study, we enrolled participants aged 60-80 years until we reached 30 total participants. Participants were randomly assigned following simple randomization procedures (computerized random numbers) to 1 of 2 treatment groups. The randomization was completed by a researcher who did not have face to face contact with the aMCI patients and the patients completed the training at home without researchers present. The patients and experimenter assessing adherence were blinded to the random group assignment. We anticipated a 10% attrition rate, in line with our previous tACS studies [1-3]. To be included in this study, participants had to be English speaking, have at least 12 years of education, have normal or corrected to normal vision (without glaucoma, macular degeneration, amblyopia, or strabismus) and hearing, be able to complete cognitive tasks and study procedures, and be able to tolerate tACS. To be categorized as md-aMCI, participants scored between 17 and 28 on the Montreal Cognitive Assessment (MoCA), had an age-matched Z score of at least -1 on immediate memory or delayed memory (as measured by the California Verbal Learning Test) *and* at least -1 Z score on verbal and semantic fluency (D words, animals), processing speed (digit symbol and number trails tasks), or task switching (number letter trails task). Finally, participants needed a self-reported memory complaint. Exclusion criteria consisted of a family history of epilepsy or seizures, serious head trauma, pregnant, any implanted electrical devices, IQ below 80, substance abuse, or on contraindicated medications that may alter brain states (anti-depressant, anti-anxiety, psychotropic medications). Of the 30 participants, 1 dropped out for personal reasons and two participants did not adhere the CCT schedule during the initial week. This resulted in 27 participants who were randomly assigned to receive theta tACS (N: 14) or control tACS (N:13). All participants signed informed consent documents approved by the University of San Francisco, California Institutional Review Board (IRB). The study took place entirely within the greater San Francisco Bay region, within individual participant's homes, as participants needed to visit UCSF on the initial day to consent, receive instructions, and equipment. Participants received $20 per hour for participation and a $50 bonus for completion of the study.

Neuromodulation

Participants were randomized to receive theta tACS (6 Hz) or control stimulation (1 Hz) using a self-applied humm tACS device (humm, California, USA). Humm tACS devices consist of a single patch with two electrodes covered in adhesive gel that fixes directly below the hairline and extends from AF3 to AF4 (10-20 EEG system). During each CCT session, tACS was applied for 15 minutes at 1.5 mA (baseline-to-peak; 3 mA peak-to-peak). Stimulation also included 30 seconds of ramping up from 0 mA to full intensity and 30 seconds of ramping down to 0 mA at the end of the 15 minutes, for a total of 16 minutes. Participants first cleansed their forehead with an isopropanol wipe where the humm device was to be applied, then pressed a button at the center of the patch to begin the stimulation. After an automated impedance check, stimulation began and then automatically ended after the prescribed 16-minute duration. Participants were provided with four humm patches as each patch was used twice across the eight stimulation sessions. The theta and control humm patches were identical in appearance and could only be identified by the serial number listed on the device, ensuring participants were blind to the existence of different conditions. Following the end of each tACS session, participants filled out a survey of side effects by rating the following 11 measures on a scale from 0 (not noticeable) to 10 (not tolerable): headache, neck pain, scalp pain, tingling, itching, burning sensation, increased alertness, increased sleepiness, trouble concentrating, acute mood change, phosphenes. Participants who rated any measure to be 7 or more would have been removed from the study; however, no participants reported ratings that would have warranted such removal. In addition to the surveys, tolerability was initially assessed in-lab during the instructional period.

Cognitive Control Training

On each of the eight CCT sessions participants began the self-applied tACS and immediately began the multitasking CCT task, *AKL-T01* (Akili Interactive Labs, Inc). AKL-T01 is a proprietary system based on patented technology underlying the NeuroRacer paradigm that challenges cognitive control by requiring multitasking performance (for more details see: [4]). Briefly, participants guide a character down a path by tilting the iPad similar to a steering wheel (visuomotor/sensorimotor task). At the same time, participants were engaged in a perceptual discrimination task, where they tapped on the screen in response to target items (e.g., green fish) and ignored all distractors (e.g., blue fish). Importantly, AKL-T01 employs algorithms that continuously adapts to individual performance in real time with feedback provided. Correctly identifying consecutive targets lowered the response time to be counted as correct, visually depicted as faster moving targets. Consecutive obstacles (gates) avoided in the visuomotor task increased the speed of the vehicle and misses slowed down the speed. Participants completed five ‘missions’ per day, which lasted approximately 20-minutes in total (i.e., 4 minutes longer than tACS). Participants received ‘stars’ as credit for multiple correct responses in a row and advanced to the next level every five stars. Participants were instructed to administer the tACS and play AKL-T01 at the same time of day during all eight CCT sessions. Participants were provided with detailed step-by-step instructions with pictures that walked them through setting up the humm devices, how to use the tablets, and the order of operations each day. Participants were also provided a calendar that listed their activities on each day over the course of four weeks. Researchers were able to remotely monitor adherence to the CCT sessions as performance data was uploaded online during each session.

Outcome Measures

Primary outcome measures consisted of 1) multitasking ability on the CCT task, 2) a sustained attention task and 3) a working memory task. On each of the three sessions where outcome measures were assessed (baseline, 1-week, 1-month), participants completed the outcome assessments on a separate color-coded iPad than the CCT task. To assess multitasking ability on the CCT task, participants completed Monitor (AKL-M01, Akili Interactive Labs, Inc), which is an assessment version of AKL-T01. Monitor consists of a set of game-like tasks lasting approximately 7 minutes in which participants were engaged in a dynamically adjusting perceptual discrimination task with and without concurrent visuospatial tracking. Similar to AKL-T01, participants completed the perceptual discrimination task by correctly tapping on the tablet's screen when the correct target appears (i.e. only green items) without having to navigate an avatar. In addition, participants completed a visuomotor/sensory motor tracking task by tilting the iPad to steer an avatar vehicle through a racecourse with obstacles present in the road that must be avoided, without having to discriminate targets. Finally, participants completed the discrimination and tracking tasks concurrently to measure multitasking abilities. Both discrimination and tracking tasks use adaptive algorithms that continuously adjust task difficulty to converge on a consistent proportional correct value, which is saved as an individual threshold of discrimination and tracking performance. These threshold values were subsequently used in statistical analyses to assess multitasking performance.

Participants also completed the Adaptive Cognitive Evaluation-Explorer (ACE-X). The tasks in ACE-X are standard tests that assess different aspects of cognitive control (attention, working memory), modified by incorporating adaptive algorithms, immersive graphics, video tutorials, motivating feedback, and a user-friendly interface. Each task within ACE-X was completed in approximately 5 minutes. Two of these tasks were sustained attention tasks used to assess attentional control, and were modeled after the Test of Variables of Attention task (TOVA). In both tasks, participants were instructed to respond as quickly as possible to a target stimulus that appeared at the top of the screen and ignore any stimuli that appeared at the bottom of the screen. Both stimuli were presented for 100 ms, had 2.1 seconds to respond, and trials occurred every 2 seconds. The two tasks differ in their proportion of target stimuli. The task with frequent stimuli (32 of 40 trials) assesses inhibitory control abilities. The task with infrequent stimuli (16 of 80 trials) assesses sustained attention abilities. There was no adaptivity of response window or feedback for these tasks to closely follow the design of the TOVA.

To assess working memory, two ACE-X tasks were used (based on the Corsi block task), which measures visuospatial working memory capacity (WM). Briefly, a field of randomly distributed diamonds appeared on the screen and participants were to tap the order (or backwards order) of the diamonds that were illuminated for 1 second each. Participants begin with three targets and if they complete two consecutive trials successfully, they advance to the next level with one additional target. If a participant fails three trials in a row, the task ends. Participants can complete up to a total of nine targets. Participant must select all target gems in the correct order within the maximum response time (5 seconds + 1 second per target).

In addition to our primary outcome measures assessing multitasking, sustained attention, and working memory, we also collected data from 4 other ACE-X tasks to be used in an exploratory analysis of other aspects of attentional control: 1) Boxed, a visual search interference processing based on the visual search paradigm [5]. 2) Color Tricker, based on the Stroop task measuring central visual inhibitory control. 3) Flanker, a peripheral visual inhibitory control task. 4) Compass, a spatial selective attention task based on the Posner cueing paradigm.

Boxed is a forced-voice task with four stimuli conditions of 20 trials each: set size of 4 or 12 and feature or congruent stimuli. The stimuli are colored landolt squares (red and green) with side openings (left, right, bottom, or top) and participants are instructed to attend to the green with top or bottom openings (target) and ignore all other red and green squares. Participants respond to whether the target has an opening on the top or bottom. The feature 4 condition includes one green target and three red distractors. Feature 12 includes 11 red distractors and one green target. Conjunction 4 includes the green target, green distractor, and two red distractors. Conjunction 12 includes the green target, six red distractors, and five green distractors.

Color tricker, based on the Stroop task, is designed to measure response inhibition performance. Participants viewed colored words that spell a color and are instructed to identify the color of the word (target) and ignore the color the word spells (distractor). The task has two conditions, congruent, matching color and word, and incongruent, mismatching color and word. In both conditions participants selected the color that matches the color of the word regardless of what is spelled. Each condition has 20 pseudorandomized trials with an equal number of targets of each color. A target color was never the word from the previous trial and a target color was never repeated two trials in a row.

Flanker is designed to measure selective attention and interference resolution performance. Participants view an array of five arrows and are instructed to identify the direction of a central arrow (target) surrounded by four flanking arrows (distractors). In congruent trials (14 trials) the center arrow points the same direction as the four flanking arrows and in incongruent trials (14 trials) the target arrow points in the opposite direction as the four flanking arrows. Trial types are mixed pseudo randomly such that no more than three trials in a row are the same condition.

Compass is based on the Posner cueing paradigm and is designed to measure spatial selective attention. Participants were instructed to look at the center of the screen where they saw an arrow pointing to the likely location of a target symbol. The task has three conditions, 40 valid trials (arrow points in correct direction), 10 invalid trials (arrow points in incorrect direction), and 10 neutral trials (arrow points in both directions). In each condition the participant tapped the side of the screen where the symbol appeared regardless of the direction the arrow was pointing. All trials are mixed pseudo randomly with no more than three of the same targets in a row (e.g. left) and no more than two invalid trials or 10 valid trails in a row.

On all adaptive ACE-X tasks, the window to respond was adaptive based on accuracy from the previous trial. This allows for the same tasks to be used in a range of participants that vary in age and clinical condition. If the participant is correct and responds quickly enough, the response window decreases by 10 ms. If the participant responds incorrectly or too slow, the response window increases by 40 ms. The minimum response window floor is 150 ms. For all adaptive modules, the inter-trial interval was 800-1200 ms and feedback occurred for 200 ms post response.

The secondary outcome measures consisted of the Instrumental Activities of Daily Living (IADL) survey, where participants rated their level of independence (independent, needs help, dependent, or cannot do) on 16 metrics (e.g. driving, managing finances, bathing) on a scale of 1 (cannot do) to 4 (independent). Mean ratings across all metrics were used for statistical analysis of IADL.

Analyses

To measure protocol adherence, we conducted independent-samples t-tests between the tACS groups on the percentage of tasks completed as compared to what was expected (CCT: 8 AKL-T01 sessions, Outcomes: 3 Monitor sessions, 3 ACE-X sessions,

3 IADL surveys). Side effects were averaged across the 8 CCT sessions per participant for each of the 11 categories. We then conducted independent-samples t-tests between the two tACS groups for each of the 11 categories.

To assess divided attention (multitasking), we measured the difficulty threshold level at each time point for both the perceptual discrimination and visuomotor tracking multitasking modules. To assess sustained attentional control, we averaged RT across both portions of the ACE-X continuous performance task (frequent and infrequent targets). To assess working memory, we averaged the maximum span correctly achieved on the forwards and backwards span tasks. To assess inhibitory control on the Flanker and Color Tricker tasks, we measured the average rate correct score (RCS) together for all trial types, which was defined as the number of overall correct trials divided by mean response time. To assess attentional orienting on the Compass task, we analyzed RCS across all trial types together. To assess visuospatial search on the Boxed task, analyzed RCS across all trial types together. For all outcome measure comparisons, we conducted repeated-measures ANOVAs (rm-ANOVA) using JASP, with a within-subjects factor of time (baseline, 1-week, 1-month) and a between-subjects factor of tACS group (theta or control). A Greenhouse-Geisser correction was used when appropriate. Effect sizes in ANOVAs are reported as partial eta squared (η^2_p) and with Cohen's d for independent samples t-tests. Post-hoc comparisons within rm-ANOVAs were Bonferroni-corrected.

References

[1] Kueider AM, Parisi JM, Gross AL, Rebok GW. Computerized cognitive training with older adults: A systematic review. PLoS One 2012. https://doi.org/10.1371/journal.pone.0040588.

[2] Reinhart RMG, Nguyen JA. Working memory revived in older adults by synchronizing rhythmic brain circuits. Nat Neurosci 2019;22:820–7. https://doi.org/10.1038/s41593-019-0371-x.

[3] Wei J, Zhang Z, Yao Z, Ming D, Zhou P. Modulation of Sustained Attention by Theta-tACS over the Lateral and Medial Frontal Cortices. Neural Plast 2021;2021. https://doi.org/10.1155/2021/5573471.

[4] Anguera JA, Boccanfuso J, Rintoul JL, Al-Hashimi O, Faraji F, Janowich J, et al. Video game training enhances cognitive control in older adults. Nature 2013;501:97–101.

[5] Treisman AM, Gelade G. A feature-integration theory of attention. Cogn Psychol 1980.