

Parent Study Title: Patient-Centered NeuroRehabilitation (PCN)

Sub-study Title: A randomized, double-blind, sham-controlled pilot investigation of the efficacy and tolerability/safety of 3 mA transcranial direct current stimulation (tDCS) in healthy older adults

Protocol Amendment Number: 01	Original Authors: <i>ARF, JR, BMH</i> Issue Date: 22 September 2016
Protocol Amendment Number: 02	Protocol updated to reflect closure to recruitment and statistical analysis methods utilized. Authors: <i>ARF, JR, BMH</i> Date: 25 April 2018
Clinical Trials.gov: Secondary Registry Numbers: Sources of Support:	NCT03034954 (first registered 24 October 2016) UMIRB: IRBMED HUM00111090.1 This project was supported by the NIH/NIA funded Michigan Alzheimer's Disease Center (P30AG053760)
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Trial Sponsor: Address:	University of Michigan, Michigan Alzheimer's Disease Center 2101 Commonwealth Blvd., Suite C Ann Arbor, MI 48105 (734) 763-9259
Public Title:	Patient-Centered NeuroRehabilitation
Countries of Recruitment:	United States of America
Problem(s) Studied:	Healthy aging, memory loss, cognitive decline
Intervention:	Active Comparator: 3 mA High Definition Transcranial Direct Current Stimulation (HD-tDCS) Placebo Comparator: Sham HD-tDCS
Key Inclusion Criteria:	Ages eligible for study: ≥ 50 years right-handed, first-language English, no psychiatric or neurologic conditions/diseases, human volunteers with no cognitive impairment
Key Exclusion Criteria:	Neurologic or psychiatric diagnosis; dementia or MCI diagnosis, select implants in the head or neck
Study Type:	Interventional, parallel groups Randomized double-blind, sham-controlled Primary purpose: evaluate efficacy on specific cognitive domains, establish tolerability, blinding data; Phase: Not Applicable
Date of First Enrollment:	October 2016
Target Sample Size:	40
Recruitment Status:	Closed to Recruiting
Primary Outcomes:	Performance on a spatial memory test; performance on n-back working memory test
Secondary Outcomes:	Tolerability/safety of stimulation; effective blinding to stimulation

Roles & Responsibilities - Contributorship

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Roles & Responsibilities:

Design conception and initiation
Managing correspondence with clinical trials office
Publication of study reports
Preparation of manuscripts
Randomization preparation

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Refinement of study design
Preparation of protocol and revisions
Recruitment and screening of patients
Data collection
Data entry, verification
Statistical Analyses
Preparation of manuscripts

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Statistical Analyses
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Roles & Responsibilities:

Preparation of case report forms
Managing correspondence with clinical trials office
Reporting of serious unexpected suspected adverse events and annual risk reporting
Budget administration

BMH conceived of the study and initiated the study design. *ARF* and *JR* assisted in refining the study protocol and are responsible for study implementation, including data collection, entry, and management. *ARF* and *JR* are completing statistical analyses and will act as primary authors on resulting manuscripts, under the supervision of *BMH*. *AB* assisted in managing clinical trial registry, preparation of institutional review board application, administrative duties, database and participant management, as well as audit and reporting paperwork to the various agencies associated with the study.

Roles & Responsibilities – Sponsor(s)/Funder(s)

This project was supported via a pilot grant (to *BMH*) from the NIH/NIA funded Michigan Alzheimer's Disease Center (P30AG053760). The funding source had no role in the design, execution, analyses, or interpretation of the study, nor will it have a role in the decision to submit results.

Introduction

Background & Rationale

"Normal" aging is associated with declines in learning and memory, such as losing or misplacing personal items, a complaint often reported by older adults. These complaints parallel neurological changes that occur in late-life; for example, the specific complaint of misplacing household items, known as a failure in object location association (OLA) memory, relies on several brain regions, including frontal, parietal, and medial temporal regions, that work together to bind object and location information into long-term memory (Postma et al., 2008; Gillis et al., 2016; Hampstead et al., 2016). We previously demonstrated overlap in the same frontoparietal regions involved in OLA memory and working memory (Gillis et al., 2016). The current pilot study investigates whether a single session of High Definition transcranial direct current stimulation (HD-tDCS) affected performance on one, or both, of these cognitive abilities.

HD-tDCS modulates neuronal excitability and is generally considered safe and well tolerated. This method offers improved focality relative to the standard pad-based approach to tDCS (Edwards et al., 2013; Datta et al., 2009). Our recent safety review revealed that about 96% of tDCS sessions used some variant of 1 or 2 milliamp (mA; Bikson et al., 2016). The arbitrary cap at 2 mA has no theoretical or empirical justification, since available evidence suggests a current intensity of 167 mA (or greater) would be needed to induce tissue damage. Thus, the current pilot study will use a current intensity of 3 mA in order to evaluate the effects on cognition while also evaluating tolerability and safety of this under investigated dosage.

tDCS Safety Considerations. According to a review encompassing tDCS studies conducted through 2016, tDCS is a safe intervention with no reported cases of severe or unexpected adverse events, tissue damage, or irreversible brain injury in over 33,200 conventional sessions (duration \leq 40 minutes, current \leq 4 mA; Bikson et al., 2016). Furthermore, no serious adverse events have been reported in 'vulnerable' populations, including children, older adults, and individuals with epilepsy, stroke history, or implanted devices (Bikson et al., 2016). There is little evidence to indicate that higher dosage of intensity or duration is unsafe (Bikson et al., 2016).

Assuming that an absence of a reported event in a study equates to no event occurring, 56% of published tDCS studies report any type of adverse event/effect (Brunoni et al., 2011). The few side effects reported by patients are comparably experienced in those receiving active and sham tDCS and include sensory experiences like itching, tingling, headache, burning, or discomfort at the electrode placement site on the scalp (Brunoni et al., 2011). This study will use the standardized side effect questionnaire provided by Brunoni and colleagues (2011) to evaluate such sensations.

Objectives & Hypotheses of the pilot study

Objective 1: To assess the efficacy of HD-tDCS on OLA memory and working memory in cognitively intact older adults. The study will randomize participants to active or sham HD-tDCS and apply 3 mA over the lateral prefrontal cortex, given this area's role in both OLA and working memory tasks (Gillis et al., 2016). We predict improved performance on both tasks in those receiving active relative to sham HD-tDCS. While we will perform statistical contrasts, particular attention will be paid to measures of effect size given the preliminary nature of the study.

Objective' 2: To evaluate tolerability and blinding of tDCS at 3 mA stimulation in cognitively intact older adults. Establishing such data will fill key knowledge gaps in our understanding of such information at current intensities above 2mA. Based on available evidence (Bikson et al., 2016);

Brunoni et al., 2011), we predict comparable side effect profiles between active and sham and that the groups will be no different in determining stimulation status (i.e., active vs. sham).

Trial Design

The study uses a randomized, sham-controlled, double-blind parallel groups design. All participants will be randomized to receive 20 minutes of active or sham stimulation. Sham consists of a 30-second 'ramp-up' period to 3 mA followed by a ramp down period of 30 seconds that occurs in the first and final minute of the session. Participants will not be told to which group they were assigned. Two study staff (*ARF* & *JR*) will conduct the stimulation and behavioral outcome/tolerability, safety, and blinding measures separately to maintain examiner blinding. For more information regarding design, see *Methods* section.

Methods: Participants, Interventions, & Outcomes

Power Analysis

We conducted an *a priori* power analysis for two-tailed mean comparisons between Active and Sham participants on OLA and working memory measures (see Measures section below), based on the estimated effect size from a meta-analysis of single-session anodal tDCS to the dorsolateral prefrontal cortex (DLPFC) of healthy adults (Hedges $g = 0.254$ for sham vs. tDCS accuracy effects; Brunoni and Vanderhasselt., 2014). At a power level of 0.80, the required sample size to achieve an effect size of 0.25 was 10 participants per group; therefore, we will recruit at least 30 total participants (15 per group) to ensure adequate power.

Participants

Participants will include 40 right-handed, cognitively intact, community-dwelling older adults, age 50+. Participants will be recruited from the University of Michigan Neuropsychology Clinic, the Michigan Alzheimer's Disease Center, the University of Michigan Health Research Registry and the surrounding community. All study-related activities will occur at the University of Michigan.

Inclusion Criteria

Those participants who have recently undergone testing demonstrating no significant cognitive impairments (Mini-Mental Status Exam [MMSE] score > 23 within last six months) will be accepted into the study. For potential participants without recent cognitive testing, we will perform the MMSE following informed consent in order to establish cognitive status. All participants are also screened to ensure that they meet criteria to participate. All participants received \$10 for participation in the study.

Exclusion Criteria

General exclusion criteria include a history of traumatic brain injury (by patient report or available medical record), diagnosed neurologic disease (including Parkinson's disease, dementia, epilepsy, multiple sclerosis, or tumor), severe mental illness (e.g., bipolar disorder, schizophrenia, other psychotic disorder), substance use disorders, and cognition-impacting medications (anticonvulsants, antipsychotics, anxiolytics). Individuals with skull plates or other implants impacting tDCS current flow will not be enrolled in the study. Individuals with significant visual impairments that limit ability to see stimuli, or motor impairments that may interfere with ability to participate in the touchscreen task will also be excluded. To ensure appropriate electrode-scalp contact required for stimulation to be safely and effectively administered, participants with scalp dermatitis or limiting hair styles will be excluded. To clarify future interpretation of results, individuals with significant alcohol or recreational drug use or poor sleep within the 24-hours prior to the stimulation session will be excluded from the study. Individuals currently participating in other neuromodulation studies are not eligible to participate.

Recruitment Strategy

Participants will be recruited from the University of Michigan Neuropsychology Clinic, the Michigan Alzheimer's Disease Center, the University of Michigan Health Research registry, and the surrounding community. Three methods will be used to identify potential participants. First, researchers will engage in prospective recruitment for older adults who meet inclusion criteria. This will rely on provider referral in which the provider will 1) give the patient an approved flyer or 2) ask the patient if the provider may inform research staff of his or her interest via in-person contact, telephone, or UM email. Flyers will be posted within the clinic. Second, participants will be recruited through the University of Michigan Alzheimer's Disease Center (MADC). The MADC recruits participants from several sources including the MADC Memory Disorders clinic, community screening events, and external referrals. Participants interested in research are maintained in an IRB-approved database (IRB# HUM00000382), which is available to the PI and his study team. Third, researchers will post an approved description of the study to the University of Michigan Health Research registry, and contact participants who indicate interest in participation for further screening.

Procedures

Participants will complete a single, (roughly) two-hour-long session involving either active or sham stimulation and computerized cognitive tasks. All sessions will take place in the PI's (Hampstead) laboratory at the University of Michigan. Individuals will receive \$10 compensation for their participation in the study, paid via check after the session.

Randomization

Randomization will use the sealed envelope method in which group assignment is placed in a sealed envelop (by PI *BMH*) and then envelopes are shuffled and numbered. The study team member (*ARF*) will open the envelope directly before the stimulation phase of the session, ensuring the other team members remain blinded, and provide the designated treatment condition. Only one team member will be in the room at this. The team member not overseeing stimulation will return after the 20-minutes have been completed and will administer the side effect questionnaire and the cognitive tests. For further clarification of timing of procedures and study team involvement, see Figure 1.

Interventions

HD-tDCS. Participants will undergo a single session of active or sham 4x1 high-definition transcranial direct current stimulation using a Soterix 1x1 TES device and attached 4x1 Multichannel Stimulation Adaptor. HD-AtDCS uses small gel-based electrodes (as opposed to conventional tDCS, which uses large, fluid-soaked sponge electrodes) to deliver a more localized current to specific brain regions. The montage is designated 4x1, as it utilizes a central electrode that defines the polarity of the stimulation (anodal in the current study), surrounded by four return electrodes that constrict the area of excitability. In order to target OLA memory, researchers will employ stimulation under the anode placed over the left lateral prefrontal cortex at the inferior frontal gyrus (F5 in the 10/20 International system). Participants undergoing active stimulation will receive 20 minutes of stimulation at 3 mA. Conversely, participants undergoing sham stimulation will receive a 10-second ramp-up, 30-second stimulation at 3 mA, and 10-second ramp-down, followed by approximately 19 minutes without stimulation, and a second ramp-up/ramp-down period. These short periods of stimulation are completed for effective blinding of participants. Step-by-step procedures for HD-tDCS set-up and stimulation are detailed below under 'Participant Timeline of Procedures'.

Primary Outcomes

Object Location Touchscreen Task (OLTT; Hampstead et al., 2011; England et al., 2015).

Participants will undergo the OLTT, an ecologically relevant measure of object location association

memory. The OLTT requires participants to learn and recall the location of 15 object-location associations. Memory is evaluated using a touchscreen monitor, which allows for the continuous measurement of memory accuracy (i.e., distance from targeted location).

N-Back Working Memory Tasks. The n-back is a well validated measure of working memory. Participants will complete the same n-back paradigm, which includes 0-back and 2-back conditions, as in our earlier study (Gillis et al., 2016). Additionally, a semantic 2-back condition will be used that requires participants to state whether a given object is of the same semantic category as the one presented two items ago.

Secondary Outcomes

Tolerability

Immediately following stimulation, participants will complete an adapted form of the side-effect questionnaire developed by Brunoni and colleagues (2011; see Figure 1). We will delay examining the skin for redness until after the participant has completed the condition estimate (see below) in order to avoid any potential bias that could impact blinding. For further information on safety monitoring plan, see the 'Methods: Monitoring' section below.

Effectiveness of Blinding

After completing the side-effect questionnaire, participants will be asked to state which stimulation condition they believed they received (referred to as "condition estimate" in this document; i.e., active/"real", sham/"fake", or "I don't know").

Participant Timeline of Procedures

1. Participants will complete an initial telephone screening prior to ensure basic eligibility. Participants who meet inclusion criteria will be scheduled for a two-hour appointment within approximately one week of initial screening (allowing for the participant's schedule).
2. During the study session, participants will first provide informed, written consent. Additional background and screening questions regarding medical history, acute sleep problems or alcohol use, and other eligibility criteria will be recorded. If not completed within the six months prior to the session, an MMSE will be completed. If additional concerns remain regarding participant eligibility, study team members will confer with *BMH*. If a participant is deemed ineligible at this stage, he or she will still receive the financial compensation for participation, but will be dismissed.
3. Eligible and enrolled participants will begin study procedures by completing the OLTT (Version B).
4. During the 15-minute break between encoding and retrieval, two study team members will measure and mark the electrode locations on the participant's head. A mesh cap will be placed over the participant's scalp and plastic electrode holders placed over the marked locations. Hair will be moved out of the way of these electrode holders, exposing as much scalp as possible. Each holder will be filled with conductive gel and checked for air bubbles using a plastic syringe. Each electrode will be lowered into place using the syringe, and electrode holder caps will be secured into place to eliminate movement of the electrodes during stimulation.
5. Immediately following electrode placement, first impedance values will be checked as noted above. During a 10-minute saturation period, participants will complete the OLTT Version B. These results will serve as a relative baseline against which post-stimulation OLTT measures are compared. Immediately following the end of the 10-minute saturation period, a second set of impedance readings will be taken. Electrode resistance or impedance readings of less than or equal to 2.0 quality units have been used in previous studies as suggested goals for contact

quality (Villamar et al., 2013); if any impedance reading exceeds this cut-off, examiners will repeat and check electrode placement as needed (moving additional hair away from the scalp, filling any air bubbles in gel) to reduce impedance to acceptable levels.

6. At this time, one study team member (*JR*) will leave the room to remain blinded to stimulation condition. The second study team member (*ARF*) will open the next sealed, opaque randomization envelope (prepared in advance by *BMH*; see 'Randomization') to reveal the condition assignment, concealing this information from the participant. The study team member (*ARF*) will make adjustments to the HD-tDCS unit to prepare for sham or active stimulation.
7. The participant will then begin 20-minutes of the assigned active or sham stimulation. Exactly 10 minutes after the beginning of stimulation, the participant will begin encoding trials of a novel version of the OLTT (Version C), as various studies have shown that online (during stimulation) encoding may produce more robust learning and memory effects. *ARF* will note the time at which encoding is completed, beginning the 15-minute delay timer.
8. Immediately after completion of stimulation, *ARF* will take a final, post-stimulation impedance reading. All HD-tDCS units will be turned to the default settings and removed from view. Electrodes and mesh netting will be left on to maintain blinding of the participant and other staff members.
9. In order to avoid the potential for biased behavior while recording outcomes and to maintain blinding, *ARF* will then exit the room; *JR* will return to complete outcome measurement.
10. When the 15-minute delay timer has expired, the participant will be asked to complete the memory portion of the OLTT Version C, followed by the N-Back tasks, the side effects questionnaire, and finally the condition estimate. This sequence and timing of outcome measures is critical not only for blinding, but also to capitalize on the presumed timing of effects of HD-tDCS (drawn from Kuo et al., 2012).

Figure 1 depicts the general sequence of these study session; Figure 2 depicts the timing of stimulation and outcome measurement in greater detail.

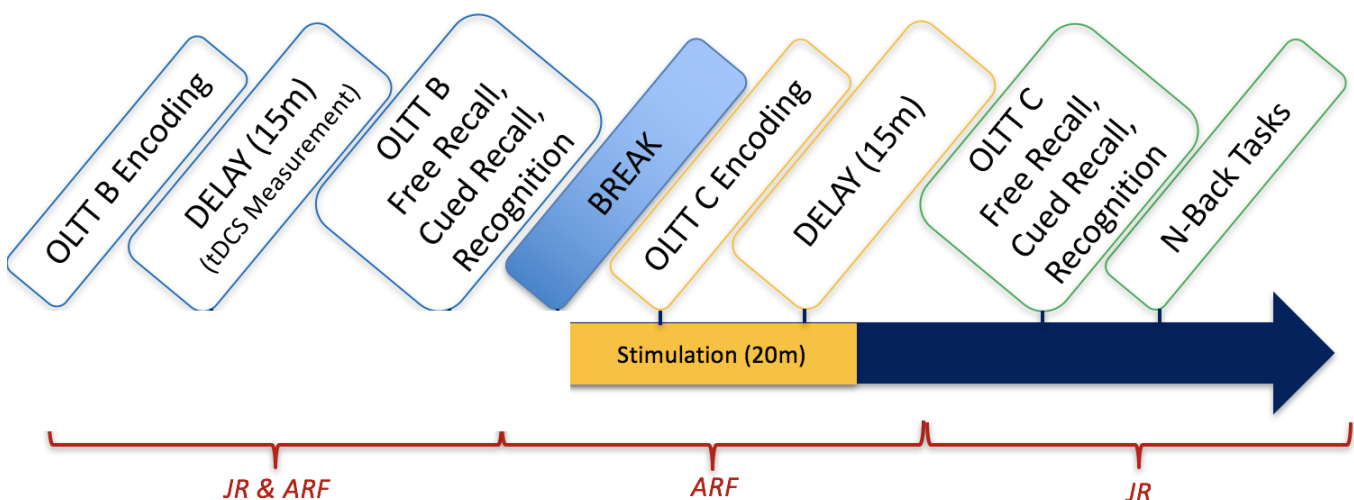


Figure 1. General Sequence of Study Session Procedures

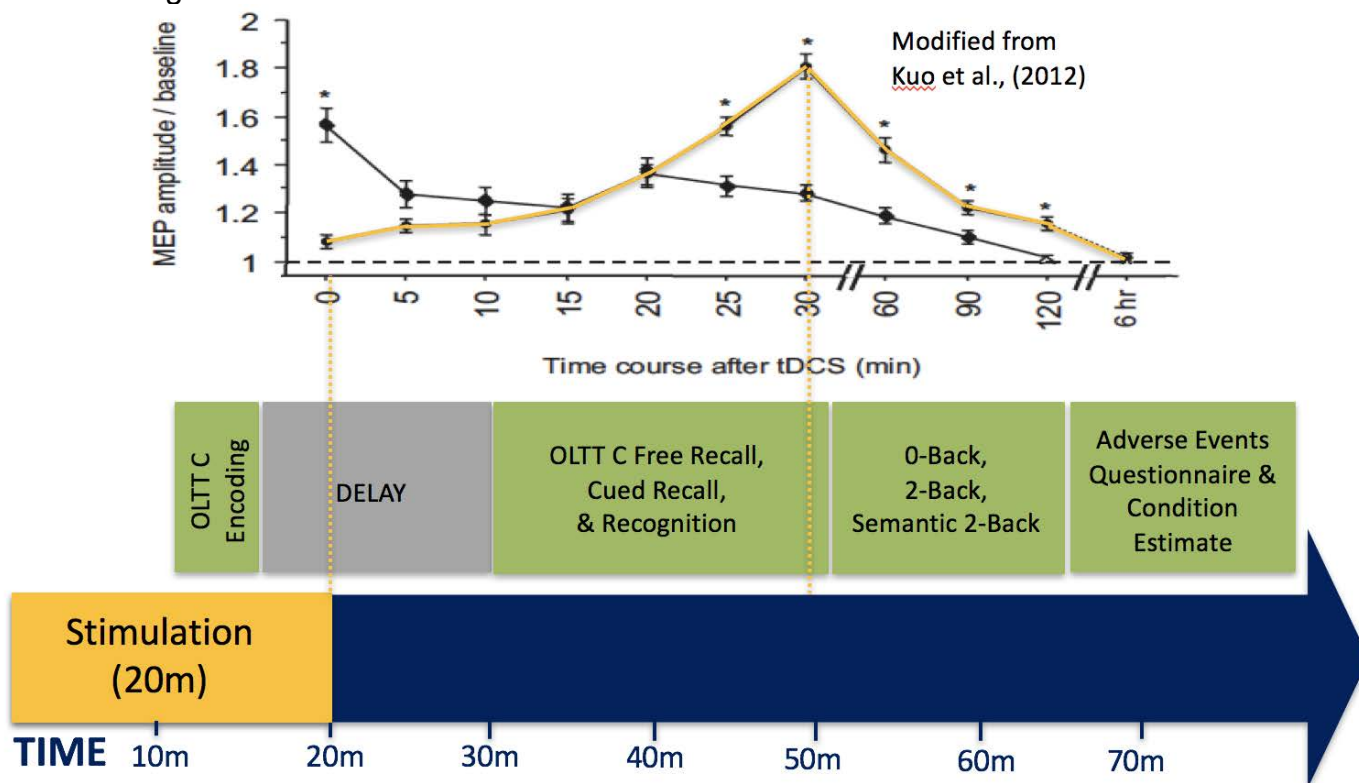


Figure 2. Proposed Timeline for Stimulation, Cognitive Tasks, Side Effect Questionnaire, and Condition Estimate

Methods: Data Management & Analysis

Data Management & Entry

Only IRB approved study personnel will have access to study documents/data. Consent paperwork and any other identifying information provided by the participant will be uploaded into the patient's medical record according to IRB standards and then stored in a binder, separate from all other study data. Data are kept in a locked file cabinet within a private office in an office suite (i.e., behind two locked doors). The participant's study ID number will be recorded on every paper page of the study documents.

Separate databases containing participants' stimulation condition and outcome data will be maintained until the study is complete and closed to enrollment, at which time investigators will break the blind and combine these databases. Earlier unblinding of the participant or investigators is not anticipated, and will only occur in the case of serious adverse events. All data will be entered within 48-hours of the participant's visit, with ARF entering condition allocation data and JR entering outcome data. To maintain confidentiality of the electronic data, both databases will reside on secure University of Michigan servers, be password protected, and will only be accessible by approved study personnel.

Statistical Design

Data Screening

Prior to statistical analyses, data screening will be conducted. Initial steps will include a missing data analysis to determine randomness of missing data and range checks to assess for data quality. Of note, due to unforeseen technical issues, 2-Back Working Memory condition data were lost from the first 11 participants at the outset of the study (at random; no participant-related factors predicted this loss); investigators chose to expand the sample size by 15 participants in order to meet a priori sample sizes. Additional screening for univariate and multivariate outliers, skewness and kurtosis will be conducted to inform needs for data transformation and statistical approach.

Statistical Approach: Primary Outcomes

To compare change in performance on the OLTT Version B (pre-stimulation) and C (post-stimulation) in the active and sham groups, repeated measures analysis of variance (ANOVA) will be used. Specific outcome variables of interest will include Free Recall and Cued Recall average accuracy (in cm) and average reaction time (in ms), Recognition accuracy (number correct), and average Recognition time (in ms).

To assess group differences in N-Back performance, multivariate analysis of variance (MANOVA) was employed, comparing active and sham groups on discriminability (d'). More specifically, d' in the 2-back and Semantic-Back conditions was compared to d' in the 0-back condition as a purer measure of working memory, eliminating the influence of basic processing speed.

Statistical Approach: Secondary Outcomes

To evaluate tolerability on the side effects questionnaire, the frequency of each reported side effect will be evaluated as a function of stimulation condition (i.e., active or sham) using Fisher's Exact Tests. Any severe adverse effects will be reported following established IRB protocols (see Methods: Monitoring). To evaluate blinding, chi-squared tests will be conducted to determine group differences in actual condition assignment vs. estimated/perceived condition.

Methods: Monitoring

A study team member will be present in the room with the participant for the entirety of stimulation. Stimulation will be paused should the participant report significant discomfort; additional gel will be added to improve contact and impedance review. In the event of a participant request to discontinue stimulation, serious adverse event, or reporting of an unusual (i.e., not listed as a common side effect in the side effects questionnaire) or concerning (e.g., significant acute mood change) side effect, stimulation will be discontinued. This will be accomplished by the study team member engaging the abort button on the TES unit, which gradually ramps down stimulation until it is discontinued. This gradual but rapid reduction in stimulation is preferred to manually discontinuing stimulation by turning off the machines, as it minimizes discomfort. Study staff will immediately alert the principal investigator (*BMH*) and medical assistance as needed.

Participants will also complete the side effects questionnaire after stimulation has ended. Study team members will review all responses during and following each session and will immediately consult with the PI should moderate-to-severe ratings be reported. *BMH* has also established a relationship with a world-renowned expert in TES, Dr. Marom Bikson at the City University of New York, and will consult Dr. Bikson should any concerns arise.

Consistent with FDA and IRB guidelines, we will report severe unanticipated events associated with TES within 48-72 hours to both organizations. We will seek guidance about whether to pause study enrollment/procedures at that time.

Ethics and Dissemination

Research Ethics Approval & Protocol Amendments

This study-specific protocol falls under the larger Patient-Centered Neurorehabilitation (PCN) Study protocol. All procedures detailed above fall within the parameters approved by the University of Michigan institutional review board (UMIRB: IRBMED HUM00111090). Any changes to these parameters or procedures will be proposed to and approved by the IRB through formal amendments prior to implementation.

Consent or Assent

All consent forms and others requiring authorized signatures were approved by the University of Michigan IRB. A study team member will review the consent form, emphasizing the relevant aspects of the PCN study to be conducted during this sub-study. The team member will pause after each section to solicit and answer questions. Comprehension of the procedures, risks, benefits, and other aspects of the study will be checked using a decision-making tool (a brief measure asking the participant to use his or her own words to review the contents of each section of the consent form before signing).

Confidentiality

Information gathered from individuals contacted for initial screening is entered into a recruitment database file that is stored in the shared drive (accessible only to select, approved lab personnel) and password protected. This centralized file will contain only the necessary information for contacting and determining eligibility and interest in the study, as well as assigned ID numbers for enrolled participants. For information regarding security and confidentiality of data from enrolled participants, see '**Data Management & Entry**'.

Participants are aware prior to enrollment that they will not receive feedback regarding their performance on cognitive screening or outcome measures, nor information about their stimulation condition assignment. As mentioned above, a copy of the consent form is uploaded into the participant's University of Michigan electronic medical record as a 'Research Document' to communicate current research participation to medical providers.

Declaration of Interests

None of the study investigators have any financial or competing interests to declare.

Access to Data

Study data will remain housed within the Hampstead laboratory at the University of Michigan and will only be available to authorized study team members or members of oversight committees (e.g., IRB).

Ancillary and Post-Trial Care

As noted above, there are procedures in place to alert the principal investigator and take any needed action to deal with serious adverse events or harms that occur during the study session. As stated in the consent form, participants are instructed to seek immediate medical attention for any serious adverse events that arise after the study session, rather than waiting to contact or hear back from study personnel. Participants are instructed that any medical appointments that are attended after the study will be billed through the patient's regular insurance avenues.

As this study is examining a non-clinical sample of healthy older adults, and HD-tDCS is not considered part of the standard of care for older adults, there is no obligation to provide a waitlist control or delayed access to treatment to individuals assigned to the sham condition.

Dissemination Policy

A summary of results from the current study will be uploaded within one year of study completion to clinicaltrials.gov. At this time, there are no plans to grant public access to the participant level dataset or statistical coding used to analyze data. Findings will be communicated in the form of scientific presentations at national meetings and publications in peer-reviewed scientific journals. There are no restrictions on publications. Authorship will be based on study contribution, considering efforts towards study design, data collection and management, statistical analysis and interpretation, and production of presentations and manuscripts.

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