STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official title: High-Definition Transcranial Direct Current Stimulation on Episodic Memory in Individuals with Amnestic Mild Cognitive Impairment and History of TBI

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The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board

Protocol

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1. Introduction and Purpose:

This is a pilot study being done to attempt to improve episodic memory problems in persons with amnestic mild cognitive impairment (aMCI) and a history of traumatic brain injury (TBI). Although the hippocampus is a brain structure most often associated with episodic memory, learning and recall of new information involves a complex interplay of multiple regions in a neural circuit. The pre-supplemental motor area (preSMA) and dorsal anterior cingulate cortex (dACC) have been shown to play a role in episodic memory retrieval. Prior studies have suggested that neurostimulation of the memory circuitry can improve episodic memory recall. The purpose of this study is to examine the efficacy of high-definition transcranial direct current stimulation (HD-tDCS) to the preSMA/dACC region and its influence on episodic memory in patients with aMCI and a history of TBI. Entraining the preSMA/dACC circuit involved in episodic memory with 10 sessions of HD-tDCS will allow us to investigate whether neurostimulation may be used to improve memory functioning evaluated by neuropsychological measures. Participants will receive 10 sessions of active stimulation (1 mA anodal HD-tDCS targeting preSMA/dACC for 20 min) or sham across 2 weeks. Episodic memory tasks will be completed at baseline, immediate follow-up after session 10, and a 3-month follow-up.

2. Background:

The majority of previous research and clinical studies on neurostimulation used two electrode preparations, involving tDCS which has a large cathodal and an anodal electrode, arranged so that applied current would pass through a targeted region. However, HD-tDCS makes it possible to stimulate more focal areas and with more precision. HD-tDCS has been shown to produce plastic changes that may outlast conventional tDCS. Compared to tDCS, HD-tDCS achieved electrical fields with greater focality (80% improvement) and higher target intensity (98% improvement) at cortical targets using the same total current applied.

Hart and colleagues studied TBI patients who were Operation Enduring Freedom and/or Operation Iraqi Freedom (OEF/OIF) combat veterans with cognitive deficits and assigned them to receive active or sham HD-tDCS over the preSMA/dACC region. A total of 10 (20-minute) sessions were administered, one each day over 2 weeks (10-14 days), for both the sham and active conditions. At baseline, immediate follow-up, and 8-week follow-up, a neuropsychological test battery was administered. At immediate follow-up, HD-tDCS compared to sham led to a significant increase in items recalled on the episodic memory measure, as well as better performance on a measure of complex attention. Up until now, research stimulating the pre-SMA/dACC has primarily focused on improving functions in patients with acquired brain injuries. This study hopes to explore the ability of the HD-tDCS device to enhance cognitive functions in adults at high risk for developing dementia following a history of TBI.

Previous research in patients and healthy adults have shown that repeated neuromodulation sessions over consecutive days is safe and led to improvements in functioning.

3. Concise Summary of Project:

The research objective of this study is to examine the efficacy of HD-tDCS to the preSMA/dACC region and its influence on episodic memory in patients with aMCI and a history of TBI after 10

sessions of HD-tDCS. Information collected to address this objective come from commonly used measures. All research activities will be taking place on UTSW campus. Participants will receive 10 sessions of HD-tDCS targeting the pre-SMA/dACC. Before the first, immediately after the last, and 3 months after the last HD-tDCS session the participant will complete neuropsychological measures.

4. Study Procedures:

Overview and design

We plan to recruit 24 English-speaking participants aged 50 years and older with aMCI and a history of TBI, all of whom have problems with episodic memory. Participants can be referred from identified providers at UT Southwestern Medical Center, Parkland Health & Hospital System, Veteran's Affairs Hospitals, or other locations in the DFW area with providers that are aware of this research effort. All recruitment procedures will take place at UTSW locations, as well as all research visits. All participants will have at least 12 years of education and a history of TBI as determined by VA/DOD criteria. Participants will be randomized into an active HD-tDCS condition or a sham condition with a 2:1 ratio of active (n=16) to sham (n=8) participants in order to assess the efficacy of HD-tDCS on improving episodic memory. The proposed study will measure response to treatment with 1 ma anodal HD-tDCS over the preSMA/dACC region when compared to sham. Participants will receive 10 sessions of active stimulation (1 mA anodal HD-tDCS targeting preSMA/dACC for 20 min) or sham across 2 weeks. Episodic memory tasks will be completed at baseline, immediate follow-up after session 10, and a 3-month follow-up.

Visits

Below is a table summarizing the study visits followed by a detailed description of the procedures for each visit. It is a 12 day study with a follow-up session twelve weeks after the last day.

TABLE 1. SUMMARY OF VISITS		
Visit	**PROCEDURES**	**TIME**
Visit 1	Pre-testing neuropsychological assessment	1 hour
Visits 2-10	HD-tDCS active or sham stimulation	30 minutes
Visit 11	HD-tDCS active or sham stimulation and post-testing neuropsychological assessment	1 hour 30 minutes
Visit 12	12-week follow-up assessments	1 hour

Visit 1: Pre-testing neuropsychological assessment (approximately 1 hour)

Assessments: At UTSW's Cognitive and Memory Disorders Clinic, participants will first be asked to complete the Ohio State University TBI Interview Method (OSTBIIM) to characterize TBI history and severity. Afterwards, a neuropsychological evaluation will be completed consisting of the following measures:

1. Hopkins Verbal Learning Test-Revised (HVLT-R)
2. Brief Visuospatial Memory Test-Revised (BVMT-R)
3. Controlled Oral Word Association Test
4. Wechsler Adult Intelligence Scale-IV Digit Span
5. Trail Making Test
6. Stroop Color and Word Test
7. Beck Depression Inventory-2
8. Ohio State University TBI Interview Method (OSTBIIM) to characterize TBI history and severity

Visits 2-10: HD-tDCS active or sham stimulation (approximately 30 minutes)

HD-tDCS Device: A Starstim 8-channel system is used in the study for delivery of HD-tDCS. This system is manufactured by Neuroelectrics® in Barcelona, Spain and is wireless and completely computer driven, running on a laptop using specialized software that allows for building customized stimulation protocols. The device attaches to a neoprene EEG cap having 39 predefined and annotated positions based on the International 10-20 EEG system for various electrode montages. Each position allows for insertion of a 12 mm diameter Ag/AgCl disc electrode that can be filled with a conductive gel for delivery of stimulation protocols.

Description for the Study: This specific device will be applied as a treatment to evaluate its efficacy in improving episodic memory functioning in individuals with amnestic mild cognitive impairment and a history of traumatic brain injury. A low level current (1mA) will be delivered to participants in the active condition versus 0 mA for the sham condition, through circular electrodes (12-mm in diameter) filled with conductive gel placed in a 4x1 ring configuration. The locations for electrode placement will be identified on the scalp using an EEG cap based on the International 10-20 EEG system. The preSMA/dACC region will be targeted, by placing the anode over Fz surrounded by 4 cathodes placed at FPz, F7, F8 and Cz.

HD-tDCS Stimulation Protocol: Participants will receive sessions of either active stimulation (1 mA anodal HD-tDCS targeting preSMA/dACC for 20 min) or sham across 2 weeks. Electrical stimulation will be performed using a constant voltage cortical stimulator (Model D185, Digitimer Ltd, UK, maximal output 1000 V/1.5 A) with single square-wave 50-μs pulses (0.1 A/μs rise time). An exit questionnaire given at the end of each visit for reporting and discomfort with tDCS. After each session, patients will be administered a standard post-treatment symptom questionnaire (e.g., assessing for skin irritation).

For the active condition, administration parameters will consist of the stimulation being ramped up over 60 seconds until it reaches 1 mA, maintained for 20 minutes, and then ramped down over 60 seconds at each session. The anode will be placed over Fz according to the International 10-20 EEG system, corresponding to the approximate location of the preSMA/dACC. Four return cathodal electrodes will be placed approximately 5 cm radially from Cz; corresponding to locations Fz, FPz, F7, F8 and Cz. 20 minutes of 1 milliamp of anodal HD-tDCS per session.

For the sham condition, parameters will consist of current being ramped up over 60 seconds until it reaches 1 mA and then stopped. (This allows for the same scalp sensation for both the sham and active condition so that subject and experimenter will remain blinded). This ramp up for one minute and then stopped and off for 19 minutes will be given each 20-minute sham session to keep the timing and subjective experience similar to the active condition.

Visit 11: HD-tDCS active or sham stimulation + Post-assessment (1 hour and 30 minutes)

HD-tDCS Stimulation: Participants will receive a final session of either active stimulation (1 mA anodal HD-tDCS targeting preSMA/dACC for 20 min) or sham. The stimulation current will gradually ramp up to 1mA during the first 60 seconds of stimulation, and remain for 19 minutes in the active stimulation group, but turned off afterwards for the sham group. Participants will also undergo the same neuropsychological assessments as in Visit 1.

Visit 12: 12-week Follow-up Neuropsychological Assessments

After 3 months from their last session, post-neuropsychological assessment will be completed to see if previously acquired gains remain over this time frame. Neuropsychological measures will be the same as in Visit 1.

Summary of Study Team's Experience Using HD-tDCS:

Our team has extensive experience in neuromodulation techniques. This ranges from repetitive transcranial magnetic stimulation (rTMS) to high definition transcranial direct current stimulation (HDtDCS). For the last 12 years, Sven Vanneste has utilized neuromodulation across a range of disorders to better understand brain functioning in tinnitus, aphasia, dyslexia, compulsive disorder, depression, vertigo, neuropathic pain, and cognitive disorders. He has also extensively published in the area of neuromodulation with over 150 publications and is a collaborator on this project. Dr. Vanneste has already collaborated with our team on multiple projects including a Veterans study using rTMS and multiple studies involving HD-tDCS with patients with multiple sclerosis and neurocognitive deficits. Dr. John Hart is the Primary investigator on the rTMS studies and has utilized neuromodulation techniques for the last 11 years with Dr. Nyaz Didehbani. Dr. Hart has several ongoing HD-tDCS studies looking to improve semantic memory across multiple populations. Dr. Didehbani was also trained on setting up and running the rTMS protocol establishing motor thresholds and treatment session for the veteran studies. She was involved with weekly neuromodulation meetings with Drs. Hart and Vanneste to learn about HDtDCS in addition to rTMS.

5. Sub-Study Procedures:

Not applicable

6. Criteria for Inclusion of Subjects:

1. Age 50 and older
2. Native English speakers
3. 12 years of education or higher
4. Active diagnosis of aMCI
5. History of TBI based on VA/DOD criteria

7. Criteria for Exclusion of Subjects:

1. TBI within the past 2 years
2. Lifetime history of stroke, transient ischemic attack, heart attack, or congestive heart failure
3. Lifetime history of epilepsy
4. Major psychiatric disorders (i.e., posttraumatic stress disorder, bipolar disorder, schizophrenia)
5. Substance use disorder
5. Has metal fragments in head
6. Taking medications that may interact with the HD-tDCS effect (i.e., amphetamines, L-dopa, carbamazepine, sulpiride, pergolide, lorazepam, dextromethorphan, D-cycloserine, flunarizine, or ropinirole)
7. Those found to be incompetent or have impaired decision-making capacity will also be excluded.

If a medical condition becomes apparent during the evaluation or follow-up that indicates an increased risk then the subject's involvement in the study will be discontinued.

8. Sources of Research Material:

A source of research material is the data registry of UTSW's Cognitive and Memory Disorders Clinic. The Clinic collects sociodemographic, apolipoprotein E, medical, and clinical information from individuals diagnosed with aMCI. We will obtain data about clinical diagnosis, date of birth, prior medical conditions, and apolipoprotein E status from the data registry. Because only a limited information about TBI has been collected in this data registry (e.g., presence/absence of TBI with LOC > or < 1 year ago), we will administer the Ohio State University TBI Interview Method (OSTBIIM) at a Study Visit to characterize each participant's TBI history and severity.

The following assessments will be completed at a Study Visit at UTSW's Cognitive and Memory Disorders Clinic for the purpose of the study:

- Episodic verbal memory will be assessed with the Hopkins Verbal Learning Test-Revised (HVLT-R). This measures rate of learning for verbal material and the amount retained after a delay.
- Episodic visual memory will be assessed with the Brief Visuospatial Memory Test-Revised (BVMT-R). This measures rate of learning for visual material and the amount retained after a delay.
- Controlled Oral Word Association Test to measure word retrieval within specific search parameters
- Wechsler Adult Intelligence Scale-IV Digit Span to measure attentional capacity and working memory.
- Trail Making Test to measure information processing speed as well as mental flexibility as part of executive functioning.
- Stroop Color and Word Test to measure information processing speed as well as selective attention and response inhibition as part of executive functioning.
- Beck Depression Inventory-2 to evaluate the extent of depressive symptomatology present.

9. Recruitment Methods and Consenting Process:

Providers around the DFW area who work closely with UTSW's researchers are a valuable source of referrals. Utilizing clinics outside of UTSW maximizes the participant pool while also providing a service to a greater population. Referral of participants may originate from identified providers at UT Southwestern Medical Center, Parkland, Veteran's Affairs Hospitals, or other locations in the DFW area with providers that are aware of this research effort. All recruitment procedures will take place at UTSW locations, though referrals may originate from clinics outside of UTSW. All research visits will take place at UTSW.

At UT Southwestern, participants will be screened/recruited from the ongoing data registry aimed to enroll individuals with aMCI and dementia into research investigations at UT Southwestern's Cognitive and Memory Disorders Clinic. This Clinic enrolls volunteers with aMCI and dementia from clinician referrals and self-referrals, of which the Principal Investigator Dr. Christian LoBue is one of the neuropsychologists.

Potential participants from the Parkland Outpatient Neuropsychology Clinic will have a diagnosis confirmed by the referring provider and will opt-in to be contacted for participation. A UTSW research team member will contact the participant (phone, email, or text) to further determine eligibility. If the participant is not under the care of the study PI or Co-I, then a research invitation letter will be sent to the potential subject prior to any telephone contact being made.

This data registry will be used to identify individuals for screening/recruitment into the study based on data collected over the past 2 years including a) active diagnosis of aMCI and b) aged 50 years or older. Individuals meeting these initial criteria will undergo telephone screening where a brief TBI interview will be administered, asking if they ever hit their head and had any symptoms of TBI as defined by VA/DOD criteria. Participants will also be screened for conditions in their medical history as well as current medications to save them time and effort from coming to UTSW to enroll in the study if they ultimately will not meet major inclusion/exclusion criteria.

Prospective participants meeting pre-screening inclusion/exclusion criteria (over the telephone) will be scheduled an appointment to review the study procedures and Consent Form. Study staff will go over the consent form in detail with the prospective participant and answer any questions about the procedures. Participants will be asked to sign the consent form provided at an in person visit if they understand the study procedures, appreciate potential risks/benefits, and desire to be involved in the

study. If, at any time, the subject wishes to withdraw from the screening and consent process, they will do so without penalty.

10. Potential Risks:

Overall, there is minimal risk of injury from participating in this research.

Risks from the HD-tDCS:
Overall, HD-tDCS has been found to be a safe, well tolerated investigational device as well as a treatment tool when used within the standard parameters. No serious adverse advents caused by HD-tDCS have been reported in the scientific literature. The research team will stop the procedure immediately if the subject chooses. Other side effects include:

- The most common side-effect of neurostimulation is temporarily local redness of the skin directly under the electrode. This disappears within 1 hour.
- Itching at the site of the electrode, passing within the hour.
- Slight feeling of dizziness when starting the stimulation occurs in a small number of patients. This takes only a few seconds and does not affect balance after stimulation.
- Very rarely, temporary skin damage may occur under the electrode. This creates a darkening of the skin, which normalizes after a week and heals. The size of such is a few millimeters. This risk is minimal.

Risks Pertaining to Loss of Confidentiality and Privacy:
Confidentiality of participants is a priority for research staff and also is presumed and must be maintained unless the investigator obtains the express permission of the subject to do otherwise. Risks from breach of confidentiality include invasion of privacy, as well as social and economic risks. Economic risks include alterations in relationships with others that are to the disadvantage of the subject, and may involve embarrassment, loss of respect of others, labeling with negative consequences, or diminishing the subject's opportunities and status in relation to others. These risks include loss of wages or income, and/or damage to employability or insurability.

Unanticipated risks:
Any experiment may involve risks that cannot be anticipated. Any identified risks will be reported immediately to UTSW IRB for further consideration.

11. Subject Safety and Data Monitoring:

In order to safeguard our participants from a breach in confidentiality, the data is coded with a unique semi-random subject identifier (URSI). All data after initial entry into the study is coded based on the participant’s number. A file containing completed questionnaires and assessments from the experimental session will be maintained with the URSI number. These files are kept in a locked filing cabinet behind a locked door. No PHI is attached to, or kept with data. Although a master list with links to subject identities will be kept only for each participant’s duration of the study, this list will be maintained on a separate password protected computer, thus making the risk of identification of a participant very unlikely. The people who will have access to the data include members of the research team. Identifiable data will not be shared with investigators outside of the research team. The data is also available to the IRB for audit purposes. Other investigators at UTSW wishing to do secondary analysis may have access to the data as well, but will not have access to any identifiable information associated with the data.

The PI, research members, and identified mentors will regularly meet to discuss how participants have tolerated study procedures. A portion of these meetings will be to review the number of participants withdrawing from the study and experiencing unanticipated problems over the course of the study. Research members will immediately inform the PI of any adverse events, and a decision will be reached on whether treatment may be needed for the participant. Adverse events will be

reported to the IRB and logged for periodic review by the research team as well as Sven Venneste, PhD, a collaborator on the study who will be monitoring HD-tDCS application and its safety. All safety precautions recommended by scientific literature, the UT Southwestern IRB, and the mentors and collaborators involved experienced in HD-tDCS will be carefully followed.

12. Procedures to Maintain Confidentiality:

We have taken a number of measures to ensure the confidentiality of the data and the safety of the participants, but we cannot guarantee confidentiality of all study data. The consent process will take place in a private room. All data from the proposed study will be identified by a numerical ID code (i.e., URSI) only, and according to institutional regulations and records policies. All data will be maintained on password protected servers and computers. The information linking the numerical ID code to identifying information will be maintained separate and secure from the data themselves. At the conclusion of the study, the list linking the ID code to identifying information will be destroyed. Any adverse events will be reported according to the policies of the Human Research Protections Program Office at UT Southwestern.

All records relating to this project will be handled and safeguarded according to standard UTSW policy for research records. To ensure privacy, all research files are stored in locked file cabinets in locked offices. The electronic database will be through REDCap, a secure, password-protected data capture system designed for handling research data.

All data will be entered and stored in UTSW's secure, online accessible, password-protected REDCap database. This will include patient identifiers such as name and date of birth, in order to allow for future events (e.g. concussions or other injuries) to be correlated to previous events. Access to the REDCap database will be limited to trained and authorized research personnel only. Passwords will be changed regularly.

All data communication between the REDCap browser and secure UTSW servers is through an encrypted secure socket layer connection. Servers are located in a Statement on Auditing Standards-70 compliant data center behind a dedicated firewall. REDCap has procedures in place for full compliance with Health Insurance Portability and Accountability Act security standards for protection of PHI. User password accounts are assigned according to user types and access roles which allow or restrict the viewing of any PHI fields. An algorithm is applied to each data element to determine if it should be considered PHI. The default determinations can be overridden if incorrectly classified as PHI. Administrative users can set up accounts for users to only view the data or set filters that limit viewing of records according to their study site. Every data modification is tracked and all views and deletions are logged so that data tampering is not possible.

The UTSW IRB that oversees human subject research will be permitted to access participant records. There may be times when we are required by law to share our study participant's information. However, the name of the participant will not be used in any published reports about this study. A copy of the consent form will be kept on record. The study data may also be presented at meetings, published in journals/books or used in classrooms for training purposes. It is possible that these data may be used for testing various future analysis tools, in hopes of finding better ways to understand the results.

In a separate and secure location we will keep basic information such as the participant's name, age and gender, personal information and imaging data. Research data created by this study will not become part of hospital or institutional medical records unless it is requested that research records be released to personal or institutional physicians.

Study personnel are not obligated to share study results with the participant.

Finally, the participant will understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to himself or herself or to others.

13. Potential Benefits:

This study may contribute to developing a new non-pharmacological method for the treatment of episodic memory difficulties in individuals with aMCI following traumatic brain injury. Given only a slight risk to participants and the greater possibility of long-term benefits to the knowledge base, the risks/benefits ratio seems reasonable.

14. Biostatistics:

Linear mixed modeling (LMM) will be used to assess performance growth as a function of group (i.e., number of sessions) and assessment period. Primary outcomes will be measures of episodic memory from the neuropsychological battery. Additionally, baseline assessments on neuropsychological measures, TBI severity, use of cholinesterase inhibitors, and demographics variables will allow for assessing individual differences prior to the intervention as a predictor of response to the proposed treatment schedules. LMM will allow for testing change scores from baseline as a function of group and assessment session. Obtaining combined linear and quadratic fit parameters will allow for estimating points of asymptote in the gain functions per outcome to identify optimal delivery protocol parameters. We will use restricted maximum likelihood estimators (ReML) of the variance components to compute the maximum likelihood estimators of the fixed effects parameters (i.e., group, session, and group*session interaction effects). Thus, we will not exclude participants with missing time points. All available data on all participants who 1) meet inclusion/exclusion criteria, 2) have been randomly assigned to groups, and 3) provide baseline data will be used regardless of whether they complete the trial. (Depending on the amount of dropout, analyses also will be carried out to identify any biases in dropouts per group.)