Study Title: Treating Civilian Traumatic Brain Injury With High Definition Transcranial Direct Current Stimulation (ciTBI-HDtDCS)

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

**Protocol**

**Using High Definition transcranial Direct Current Stimulation to Treat Verbal Retrieval Deficits Secondary to Chronic Traumatic Brain Injury (HDtDCS-CTBI)**

## 1. Introduction and Purpose:

The pre-supplemental motor area (preSMA) has been shown to play a role in memory and word retrieval. Prior studies have suggested that neurostimulation targeting this region can improve word retrieval as well as other cognitive skills. Entraining the preSMA circuits with 10 sessions of neurostimulation could be used to improve cognitive functioning evaluated by EEG-based and neuropsychological measures. The purpose of this study is to examine the efficacy of high-definition transcranial direct current stimulation (HD-tDCS) to the preSMA region and its influence on EEG and neuropsychological measures in patients with chronic TBI. We also use MRI imaging to examine how baseline white matter integrity affects HD-tDCS therapeutic effects. The 3 aims of this study are 1) to determine HD-tDCS targeting pre-supplementary motor area (pre-SMA) modulatory effects on verbal retrieval function and synchronized brain activity using electroencephalography (EEG), 2) to use MRI imaging to examine how baseline white matter integrity affects HD-tDCS therapeutic effects, and 3) to establish predictive models of HD-tDCS induced changes by integrating baseline EEG and MRI measures.

## 2. Background:

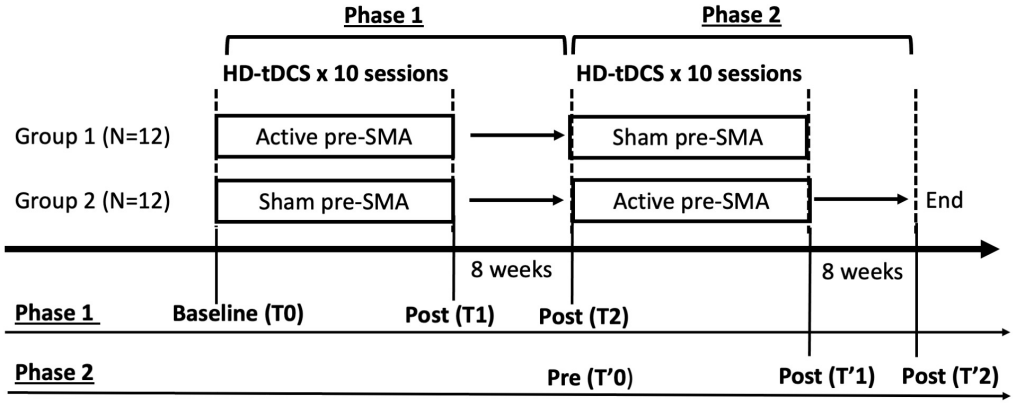
High Definition transcranial Direct Current Stimulation (HD-tDCS) represents a safe, portable, and low-cost noninvasive brain stimulation technology to target more focused brain regions and modulate dysfunctional brain circuitry underlying neurocognitive symptoms. The pre-Supplementary Motor Area (pre-SMA) is part of the neural circuit underlying word retrieval functioning and can be more easily modulated by HD-tDCS than other deeper brain structures in the circuit. We have shown in pilot studies that adults with word retrieval impairment long after traumatic brain injury (TBI) can have enhancement of word retrieval from HD-tDCS targeting the pre-SMA. Immediately following stimulation, active HD-tDCS compared to sham was associated with significant improvement on a verbal (semantic) fluency task in a small sample of adults (N=25). We later combined neuropsychological and EEG measures in a case study of a patient with word retrieval impairment 3 years after a severe TBI, and found that HD-tDCS to the pre-SMA led to enhancement of verbal (phonemic) fluency (named 36 more items than baseline) and improved frontal EEG activity that lasted for 2 months. Thus, our preliminary work indicates HD-tDCS may have the potential to improve word retrieval functioning in those with chronic TBI and that HD-tDCS induced improvement could persist for 2 months

## 3. Study Procedures:

### Overview and design

We plan to recruit at least 24 English-speaking participants aged 18-85 years with a history of chronic TBI (> 1 year since injury), all of whom have problems with cognition. Participants will be randomized into an active HD-tDCS condition or a sham condition in order to assess the efficacy of HD-tDCS on improving cognition. The proposed study will measure response to HD-tDCS treatment over the preSMA region when compared to sham. Participants will receive two phases of 10 sessions of active stimulation (1 mA anodal HD-tDCS targeting preSMA for 20 min) or sham across 2 weeks. All participants will be blinded to their condition. EEG and neuropsychological tasks will be completed at

baseline, immediate follow-up after session 10, and a 2-month follow-up. Those participants randomized into the active or sham group will have the opportunity to return after 2 months and receive sham (if active first) or active (if sham first) treatment and will undergo the EEG and neuropsychological tests again immediately following the last HD-tDCS session and at a 2-month follow-up. With this design, we expect a 15% attrition rate and plan on enrolling ~30 adults to achieve our completed sample of 24.




**Sample size justification**

Pre-study power analyses were conducted for the most power intensive phase of the study (Phase 1), using a clinically relevant effect size (Cohen's d = 1.20) derived from our prior studies. Holding 1-β=0.8, and α=0.05, a sample size of 20 would provide sufficient power to identify true interaction effects (treatment * time) across all neuropsychological outcome measures in the magnitude of f=0.27 (Cohen's d ≈ 0.54). Given that both our and other's research without intervention suggests that effect sizes tend to be larger in EEG compared to neuropsychological measures, we expect the effect size of EEG outcomes to be at least equivalent to neuropsychological outcomes. Still, we will perform an interim power analysis based on EEG data once half of the targeted recruitment is reached to ensure adequate statistical power. As the proposed sample size provides sufficient power to detect moderate effects for all outcomes, our study is well powered.

Below is a table summarizing the study visits followed by a detailed description of the procedures for each visit. It is a two Phase study. In Phase 1, participants will be randomized to active stimulation (1 mA anodal HD-tDCS targeting preSMA for 20 min) or sham and complete 13 visits. Then in Phase 2, participants who have been in the active group in Phase 1 will be invited to receive the active stimulation condition, and those who have been in the sham group in Phase 1 will be invited to receive the sham stimulation condition. Either way would involve 11 additional visits in the study.

| **TABLE 1. SUMMARY OF VISITS** | | |
|---|---|---|
| **Phase 1** | **PROCEDURES** | **TIME** |
| Visit 1 | Pre-testing neuropsychological assessment/semantic EEG | 3 hours |
| Visit 2 | Pre-testing MRI scan | 1 hour |
| Visits 3-11 | HD-tDCS active or sham stimulation | 30 minutes |
| Visit 12 | HD-tDCS active or sham stimulation and post-testing neuropsychological assessment/semantic EEG | 3 hours |
| Visit 13 | 8-week follow-up assessments/semantic EEG | 3 hours |
| **Phase 2** | | |
| Visits 14-22 | HD-tDCS sham or active stimulation | 30 minutes |
| Visit 23 | HD-tDCS active stimulation and post-testing neuropsychological assessment/ semantic EEG | 3 hours |
| Visit 24 | 8-week follow-up assessments/semantic EEG | 3 hours |

Transcranial Direct Current Stimulation (tDCS) is a non-invasive technique that requires the placement of several sensors (metal electrodes) on a special cap and saline gel on the participant's head. Very low levels of constant electrical current are delivered to specifically targeted areas of the brain via these electrodes. Contact quality and impedance levels (<10 kOhms) will be verified before each session. The same preparation is used for both active and sham conditions. After each session, subjects will be administered a standard post-treatment symptom questionnaire (e.g., assessing for skin irritation). Daily treatment lasting for 20 minutes (total of about 30-40 minutes including preparation) will be administered over 2 weeks (5 daily sessions each week), as scheduling allows. Session scheduling will depend on participant availability and availability in the lab. All treatment sessions will be held in Dr. Hart's lab at UTDallas.

Assessment sessions, including the neuropsychological test battery and the Semantic Selection and Semantic Object Retrieval EEG tasks, will be completed at baseline, after intervention session 10, and at 2-month follow-up assessments. Each assessment session lasts approximately 3 hours. Specifically, the neuropsychological testing will take approximately 1 hour and will assess skills in the areas of word retrieval, episodic memory, processing speed, executive functions, and visuospatial organization. Participants will be asked to complete a few questionnaires about emotional state and cognitive performance as well as completing computer tasks. These tests might be completed through in-person or remote online interviews. In addition, MRI scan will be obtained at baseline that include structural imaging and takes place at UTSW advanced imaging research center. Participants will also undergo event-related electroencephalography (EEG). The EEG procedure is a non-invasive technique that requires the placement of 64 sensors (metal electrodes) and saline gel on the scalp. The electrodes will record brain electrical activity while participants sit quietly in a chair and perform computer-based tasks. During the event-related EEG participants will be asked to react to visual stimuli shown on a screen using a button box. The EEG procedure will take place at the UT Dallas Callier Center for Communication Disorders, or Research and Operations Center West, both of which are in the laboratory of Dr. Hart. The EEG procedure takes nearly 2 hours.

**5. Sub-Study Procedures:**

not applicable

**6. Criteria for Inclusion of Subjects:**
- Age between 18 and 85
- Female and male subjects
- All races/ethnicities
- Fluent in speaking and reading English
- Capable of understanding and signing an informed (cognitive screening and questions on understanding of the study are included to assess capacity)
- Has had a TBI: loss of consciousness less than 24 hours, posttraumatic amnesia less than 7 days, Glasgow Coma Scale no less than 12 at the time of injury, and Glasgow Outcome Scale-Extended (GOSE) of at least 5 at the time of evaluation.
- Has a subjective complaint of verbal retrieval difficulties evaluated with the following questions. Affirmative answers of yes to two or more of these questions is considered indicative of a subjective verbal retrieval complaint:

a. Do you have trouble finding words when in conversations with others?
b. Do you have difficulty remembering lists of things when these are told to you verbally or if the items are written down?
c. Do you have trouble producing the correct name of an object when referring to it?
d. Do you have difficulty following the conversation of other people because you do not understand what people are saying? Do you have difficulty hearing? (In this case, the answer to the first question

has to be yes and the second no for this question to be considered positive for a verbal retrieval deficit.)
- Has a subjective report of word finding difficulty assessed by the Questionnaire for Word Finding Complaints, that includes 13 Likert-type questions regarding several aspects of word retrieval.

**7. Criteria for Exclusion of Subjects:**
- Lifetime major neurologic syndromes (e.g., stroke, epilepsy, brain tumor)
- Lifetime major cardiovascular conditions (e.g., heart attack, heart failure)
- Current substance use disorder
- Lifetime major psychiatric disorders (e.g., schizophrenia, bipolar disorder)
- Current sensory or physical impairment that interferes with testing
- Implanted device such as a pace maker or other neuro-stimulator
- Has metal fragments in head
- Pregnancy

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:**

Research material from questionnaires and interviews will include data about clinical diagnosis, date of birth, sex, race, education level, personal medical history, and contact information including name, address, and telephone number. Neuropsychological testing research material will involve results for word retrieval, episodic memory, processing speed, executive functions, and visuospatial organization that will be for research purposes only. EEG research material will involve (1) latency of the frontal and left fronto-temporal ERPs and (2) magnitude (spectral power) of the frontal theta (4-8 Hz) oscillatory activity, both of which will also be for research purposes only. MRI data will include MPRAGE, T2FLAIR, and DTI images. All data will be stored on password protected computers (digital data) or in a locked cabinet in a secure location (physical data) that is password protected and accessible only to study personnel. Of note, clinical information may be collected from the subjects if they undergo assessments for these in standard clinical care visits at UTSW.

**9. Recruitment Methods and Consenting Process:**

Recruitment for the civilian TBI cohort will primarily be supported by the UTSW memory, TBI, neuropsychology clinics, all following a large population of TBI patients. In addition, we will us several strategies to maximize recruitment. These will include 1) providing study-related information with colleagues at UTSW via e-newsletters and university presentations, 2) placing flyers in exam rooms and waiting areas at UTSW memory/TBI/neuropsychology clinic facilities, and 3) advertising the study on the UTSW website, our lab website and social media using e-flyers.

Prospective participants will undergo telephone screening 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 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 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. Common side effects include:

- Possible skin sensations, such as tingling, itching, and burning sensations at the site of electrodes, that resolves when stimulation is finished. When experienced, the majority of these are mild in nature with fewer than 4% of individuals describing the sensations as intense.
- Very rarely, temporary skin irritation 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.

To minimize risk, all subjects will be monitored with one-on-one direct supervision during HD-tDCS sessions. If subjects experience discomfort more than the mild tingling or itching expected during HD-tDCS and are unable to continue, the HD-tDCS session will be immediately terminated.

Risks from EEG:

- Tiredness
- Emotional discomfort

Risks from MRI acquisition:
The scanner makes a loud, banging or tapping noise while acquiring images. Participants may experience nervousness from confinement in a tight space (claustrophobia). Participants may experience some discomfort and fatigue from lying still during scanning. There are no known effects from exposure to magnetic fields, unless in the presence of the following: heart pacemaker; heart valve replacement, or aortic clips; metal fragments in their eyes, skin, or elsewhere in their body; brain clips or pieces of metal used in aneurysm surgery or intracranial bypass; venous umbrella; pieces of metal in the body resulting from work as a sheet-metal worker or welder; clips placed in an internal organ; prosthetic devices, such as middle ear, eye, joint, or penile implants o joint replacement; hearing aid that cannot be removed; neurostimulator; insulin pump; intrauterine device (IUD); shunts or stents; metal mesh or coil implants; metal plate, pin, screws, or wires, or any other metal implants

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:**

All HD-tDCS sessions will be overseen by the Co-PIs. All safety precautions recommended by scientific literature and the UT Southwestern IRB will be carefully followed. All adverse events volunteered by the subject or elicited by the research team will be recorded in the subjects' research file. All adverse events will be reported within one week to the IRB. Any severe adverse events will be

reported within 24-48 hours to the IRB. Data safety monitoring and review will be performed every six months by the research team.

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 digital file containing completed questionnaires and assessments from the experimental session will be maintained with the URSI number. These files will be stored on password in a locked cabinet in a secure location (physical data) and accessible only to study personnel. 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.

**12. Procedures to Maintain Confidentiality:**

Confidentiality will be maintained according to the highest standards. All subjects will be assigned a unique research identifier number (ID). All data will be deidentified with this ID and recorded on subject case report forms. The case report forms and key for linking coded identifiers to personal identifiers will be maintained in an encrypted UTSW IRB approved electronic data management program and on password protected computers that only designated study personnel have access to. Research data created by this study will not become part of hospital or institutional medical records. Study personnel are not obligated to share study results with the participant.

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 in a locked cabinet in a secure location (physical data) that is password protected and accessible only to study personnel. 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.

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:**

The potential benefit of this study to subjects includes the opportunity to contribute to a scientific investigation that may benefit others in the future. Benefits to others include: informing a possible new intervention for cognitive deficits in TBI. The risks associated with study procedures are no more than what would be expected in routine clinical and neuropsychological assessment and HD-tDCS applications. Thus, there is a strong benefit to risk ratio. The potential benefits to TBI subjects, scientific community, and society outweigh the risks associated with study procedures.

**14. Biostatistics:**

Mixed effects models will be used to evaluate if active HD-tDCS is associated with significant improvements over sham stimulation in neuropsychological assessments. Changes in performance from baseline to immediately post intervention (cognition in Hypothesis I) and baseline to the 2 month follow-up (Hypothesis II) will be assessed for each neuropsychological outcome measure. To test Hypotheses I and II, interaction effects among treatment group (active and sham) and time will be examined. Statistical significance will be set at $\alpha = .05$. Covariates of interest include: age, sex, ethnicity, education, use of cholinesterase inhibitors, and assignment phase. Correlation coefficient across time is assumed around 0.6-0.7 based on the literature.

Specifically, we will model each measure at the jth assessment time post-treatment from an individual subject in the ith treatment condition, $yij$, as $\boldsymbol{yij}$=μ$\boldsymbol{0}$+$\boldsymbol{I}(\boldsymbol{x})$·μ$\boldsymbol{ij}$+$\boldsymbol{I}(\boldsymbol{z})$·d$\boldsymbol{ij}$+e$\boldsymbol{ij0}$, where μ0 is the baseline mean prior to random assignment to i=1,2 conditions (1- active, 2- sham); μ$ij$ is the mean change from baseline for j=1,2 assessment times (1- immediate- [T1], 2- eight weeks [T2] post-treatment); $I(x)$ is an indicator variable for phase 1; similarly, $I(z)$ is an indicator for Phase 2 (sham-to-active vs active-to-sham conversion); and d$ij$ is the mean change from baseline for j =3,4 assessment times (3- immediate- in phase 2, 4- eight weeks [T'2] post-treatment in phase 2). Additionally, e$ij$0 is a random error term with $j$0=0,1,2,3,4, indicating baseline, post-assessment times for both Phases 1 & 2. Phase 1 & 2 errors between subjects are independent but positively correlated within subjects across time; additionally, a consequence of Phase 2 is that Phase 2 errors are positively correlated across the treatment conditions. Due to expected attrition, which will cause missingness in some (but not all) assessment times, and due to the complexity of the constraints, phases, and covariance parameterization in the linear mixed effects model above, all fixed-effect parameter estimates will be obtained by maximum likelihood and all covariance parameters for random effects will be obtained by restricted maximum likelihood (REML). All hypothesis tests will be based on t-statistics from a priori hypotheses, which are interaction contrasts of the form (μ$\boldsymbol{1j}$+d$\boldsymbol{1j}$)/2− (μ$\boldsymbol{2j}$+d$\boldsymbol{2j}$)/2 where j is understood to reflect the same assessment time regardless of phase (i.e., immediate post- OR 8 weeks post-treatment). The interaction contrast, shown above, reflects overall active HD-tDCS effects compared to sham. All analyses will be performed in SAS, R, and/or Matlab.

Mixed effects models will be used to evaluate if active HD-tDCS is associated with significant changes over sham stimulation in EEG measures. Changes from baseline to immediately post intervention (Hypothesis I - latency; Hypothesis II - magnitude) and then baseline to 2 month follow-up (Hypothesis III) will be assessed. To test Hypotheses I-III, interaction effects among treatment group (active and sham) and time will be examined. Statistical significance will be set at α = .05. Correlation coefficient across time is assumed around 0.6-0.7 based on the literature.