

AWARD NUMBER: W81XWH-20-1-0846

TITLE: Treatment of Verbal Retrieval Deficits in Mild Traumatic Brain Injury with High Definition Transcranial Direct Current Stimulation

PRINCIPAL INVESTIGATOR: John Hart, Jr., MD

CONTRACTING ORGANIZATION: The University of Texas at Dallas, Richardson, TX

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PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

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# REPORT DOCUMENTATION PAGE

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				<b>5b. GRANT NUMBER</b>	
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				<b>5e. TASK NUMBER</b>	
				<b>5f. WORK UNIT NUMBER</b>	
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b>  The University of Texas at Dallas 800 West Campbell Road Richardson, TX 75080				<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT (state purpose, scope, major findings and up-to-date report of the progress)</b> The study examines the use of HD tDCS targeting preSMA to treat word retrieval deficits in combat veterans who have suffered TBI. Qualifying participants are randomly assigned to receive 15 sessions of active tDCS (1 milliamp for 20 minutes) or sham tDCS on a schedule of 1 per day. Then, following 2- and 3-month follow-up assessments, sham participants are invited to participate in second phase of 15 active tDCS treatment sessions. At the conclusion of this study, we will have established the effectiveness of HD tDCS as a non-pharmacologic treatment for improving verbal retrieval in patients with combat related TBI. Additionally, we propose to be able to 1) classify patterns of mTBI in order to optimize HD tDCS treatment strategies, and 2) use changes in EEG as objective outcome measures of brain impairment after mild TBI and recovery of function following HD tDCS treatment.  We have established the research team, laboratory setting, and recruiting procedures, and obtained approval of all regulatory documents for the study. We screened several potential participants in the past month, and recruited our first participant to complete pre-treatment assessments in September.					
<b>15. SUBJECT TERMS (key words previously assigned to the proposal abstract or that may be significant to the research)</b> pre-supplementary motor area, transcranial direct current stimulation, traumatic brain injury, concussion, memory, verbal retrieval, word finding, executive function, electroencephalography					
<b>16. SECURITY CLASSIFICATION OF:</b>			<b>17. LIMITATION OF ABSTRACT</b>  Unclassified	<b>18. NUMBER OF PAGES</b>  10	<b>19a. NAME OF RESPONSIBLE PERSON</b> USAMRMC
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**1. INTRODUCTION:**

The study examines the use of HD tDCS targeting preSMA to treat word retrieval deficits in combat veterans who have suffered TBI. Qualifying participants are randomly assigned to receive 15 sessions of active tDCS (1 milliamp for 20 minutes) or sham tDCS on a schedule of 1 per day. Then, following 2- and 3-month follow-up assessments, sham participants are invited to participate in second phase of 15 active tDCS treatment sessions. The study is a double-blind RCT, where both experimenters and participants are blind to the assignment of treatment conditions and to the differences between phases. Participants are assessed at baseline on a neuropsychological battery and EEG tasks targeting assessment of verbal retrieval deficits and deficits in other related cognitive functions (e.g., executive function, working memory, processing speed), and then participants also are re-assessed on the battery and EEG tasks after 5, 10, and 15 sessions of treatment and at 2- and 3-months post-treatment for each treatment phase. We are targeting recruitment of 80 military veterans with remote histories of concussion, subjective verbal retrieval complaints, and confirmed object deficits on neuropsychological tests. Enrollment is open to all military veterans meeting these inclusion criteria regardless of sex, race, ethnicity, socioeconomic status, and education, as long as potential participants do not present contraindications for treatment with tDCS. At the conclusion of this study, we will have established the effectiveness of HD tDCS as a non-pharmacologic treatment for improving verbal retrieval in patients with combat related TBI. Additionally, we propose to be able to 1) classify patterns of mTBI in order to optimize HD tDCS treatment strategies, and 2) use changes in EEG as objective outcome measures of brain impairment after mild TBI and recovery of function following HD tDCS treatment.

**2. KEYWORDS:**

pre-supplementary motor area, transcranial direct current stimulation, traumatic brain injury, concussion, memory, verbal retrieval, word finding, executive function, electroencephalography

**3. ACCOMPLISHMENTS:**

**What were the major goals of the project?**

	Timeline Months	Status	% Complete
<b>Major Task 1: Pre-Study/PeriStudy Tasks</b>			
<b>1. Prepare Regulatory Documents and Research Protocol for Study</b>	1-6		
Milestone #1 – UTD IRB Approval		complete	100%
Milestone #2 – ORP/HRPO approval for protocol obtained		complete	100%
<b>2. Establishment of HD tDCS-EEG Laboratory</b>	1-6		
Obtain laboratory space, purchase HD tDCS, set-up HD tDCS, and test the unit to ensure operational. Obtain EEG equipment, set up EEG, and test the unit to be operational.		complete	100%
<b>3. Training of Staff</b>	1-6		
Staff trained in EEG and HD tDCS usage for experiments proposed.		complete	100%
<b>Major Task 2: Study Tasks</b>			
<b>1. Recruiting and Screening Patients for the Study</b>	7-33		

Milestone #3 – Completed recruiting/screening 130 patients		In process	2%
<b>2. Performing Pre-Treatment Assessments</b>	7-33		
Milestone #4 – Completion of pre-treatment assessments for 80 patients (Aims 2&3)		In process	0%
<b>3. Performing HD tDCS vs. Sham HD tDCS Treatment</b>	7-36		
Milestone #5 - Completion of treatment for 60 patients (Aim 1)		Not yet initiated	
<b>4. Perform Follow-up Neuropsychological and EEG studies of Treatment Effect</b>	13-36		
Milestone #6 - Completion of post-treatment assessments of 60 patients (Aim 3)		Not yet initiated	
<b>5. Data Analysis</b>	30-36		
Milestone #7 - Complete analyses of treatment measures (Aims 2&3)		Not yet initiated	
Milestone #8 – Complete analyses of potential staging variables (Aim 3)		Not yet initiated	
<b>6. Dissemination of Findings – Manuscript and Report Preparation</b>	30-36		
Milestone #9 – FITBIR data submitted		Not yet initiated	
Milestone #10 – Report submitted to DoD		Not yet initiated	
Milestone #11 – Abstracts and manuscripts submitted		Not yet initiated	

### What was accomplished under these goals?

Regulatory – We received UTD IRB approval in December 2020 and HRPO approval in January 2021 for the study. We are continuing to work with our FITBIR representative.

Space and Equipment – Laboratory space is established, and EEG and tDCS equipment purchased.

Training – We conducted a briefing on the protocol and training on the new tDCS equipment in early March, and the new EEG system in July. During the past quarter, we continued to refine our practices with additional training on equipment to prepare for our first enrolled participant in September.

Recruiting – We continue to grow our recruiting network and social media presence. We have promoted our project on podcasts, websites and other social media platforms. During this last quarter, we were able to resume in-person recruitment efforts and contacted over 55 organizations. In-person events attended include a resource fair at the University of Texas at Dallas, a Veteran hockey League tournament, a trip to the Patriot Paws Organization headquarters, and a visit to the DFW airport to give an informational speech to the airport police force. Our recruitment team has future recruitment events on the calendar, and we continue to correspond with previous organizations and reach out to new ones. The Covid-19 pandemic continues to have an impact on recruitment, but we are trying to minimize its effects.

### PROTOCOL (1 of 1 total):

Protocol [HRPO Assigned Number]: E01819.1

Title: Treatment of Verbal Retrieval Deficits in Mild Traumatic Brain Injury with High Definition Transcranial Direct Current Stimulation

Target required for statistical significance: 60

Target approved for statistical significance: 80

Total subjects to date: 0

**SUBMITTED TO AND APPROVED BY:**

- 10 December 2020 - UTDallas IRB Approval
- 12 October 2020 – UTSouthwestern approved Reliance on UTDallas IRB
- 12 January 2021 – HRPO Approval
- 6 January 2021 – Certificate of Confidentiality received

Amendments:

- Amendment 1 – 12 January 2021 - revised consent form to include certificate of confidentiality and clinicaltrials.gov language
- Amendment 2 – 4 June 2021 - minor revisions to protocol to clarify questionnaires for screening and clarification to the CVLT and RAVLT measure descriptions
- Amendment 3 – 28 July 2021 - strengthened recruitment by adding flyers, text for website and Qualtrics survey
- Amendment 4 – 6 August 2021 - strengthened recruitment with additional flyers and QR code

Adverse events or deviations: Nothing to Report

**STATUS:**

Recruited/Screened: 2/130

Enrolled: 0/80

In treatment: 0/60

Completed: 0/60

Demographic data of enrolled subjects: Nothing to Report.

**What opportunities for training and professional development has the project provided?**

Nothing to report.

**How were the results disseminated to communities of interest?**

Nothing to Report.

**What do you plan to do during the next reporting period to accomplish the goals?**

We will continue to focus on the AIMS and milestones 1-6 as described in the SOW. Recruiting efforts are a priority, and we will continue to actively pursue partnerships for other avenues of recruitment.

**4. IMPACT:**

**What was the impact on the development of the principal discipline(s) of the project?**

Nothing to Report.

**What was the impact on other disciplines?**

Nothing to Report.

**What was the impact on technology transfer?**

Nothing to Report.

**What was the impact on society beyond science and technology?**

Nothing to Report.

**5. CHANGES/PROBLEMS:**

**Changes in approach and reasons for change**

Nothing to Report.

**Actual or anticipated problems or delays and actions or plans to resolve them**

Covid-19 pandemic has impacted recruitment, and we are realistic about the lasting effects of the pandemic. We are monitoring the number of Covid-19 cases in our area, following local and CDC guidelines, and conducting screening and testing protocols on-line where possible. Other safety measures include reconfiguring space for social distancing, wearing masks, gloves and goggles, providing access to hand washing or hand sanitizing stations, reducing touch points, and adding additional cleaning procedures.

While we are now able to recruit, there are other issues related to Covid-19 that reduce ease of enrollment including lack of scheduled meetings/events to recruit from, continued reticence from subjects to participate in “in-person” studies, and persistent elevated infection rates in the region. We are constantly working to improve recruitment and reach our overall recruitment goals, and we are putting extra effort into recruitment efforts to adjust for delays.

**Changes that had a significant impact on expenditures**

There has been some delay in spending, particularly on staffing and participant payments, because of the delay in recruitment.

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

- Significant changes in use or care of human subjects – Nothing to Report.
- Significant changes in use or care of vertebrate animals – Nothing to Report.
- Significant changes in use of biohazards and/or select agents – Nothing to Report.

## 6. PRODUCTS:

### Publications, conference papers, and presentations

- **Journal publications** - Nothing to Report.
- **Books or other non-periodical, one-time publications** - Nothing to Report.
- **Other publications, conference papers and presentations** - Nothing to Report.

### Website(s) or other Internet site(s)

Nothing to Report.

### Technologies or techniques

Nothing to Report.

### Inventions, patent applications, and/or licenses

Nothing to Report.

### Other Products

Nothing to Report.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### What individuals have worked on the project?

Name: John Hart, Jr., MD, Principal Investigator, UTDallas – no change

Name: Michael Motes, PhD, Project Role: Co-Investigator, UTDallas – no change

Name: Jeffrey Spence, PhD, Project Role: Co-Investigator, UTDallas – no change

Name: Elizabeth “Ellen” Morris, PhD, Project Role: Research Study Coordinator, UTDallas – no change

Name: Jill Ritter, Project Role: Research Manager, UTDallas – no change

Name: Kelsey Watson, Project Role: Research Assistant, UTDallas – no change

Name: Justin Jacqmain, Project Role: Research Assistant, UTDallas – no change

Name: Tyler Rawlinson, Project Role: Veteran Outreach Coordinator/Research Assistant, UTDallas – no change

Name: Michael Kraut, MD, PhD, Project Role: Co-Investigator, PI at Johns Hopkins University – no change

Name: Christian LoBue, PhD, Project Role: Co-Investigator, PI at UTSouthwestern – no change

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to Report.

**What other organizations were involved as partners?**

Organization Name: UT Southwestern Medical Center

Location of Organization: Dallas, TX

Partner's contribution to the project: Collaboration; subaward on project

Organization Name: The Johns Hopkins University

Location of Organization: Baltimore, MD

Partner's contribution to the project: Collaboration; subaward on project

**8. SPECIAL REPORTING REQUIREMENTS**

**COLLABORATIVE AWARDS:** Not applicable

**QUAD CHARTS:** Attached

**9. APPENDICES:**

Nothing to Report.

# Treatment of Verbal Retrieval Deficits in Mild TBI with HD tDCS



Log Number: PT190081

Award Number: W81XWH-20-1-0846

PI: John Hart, Jr., MD Org: The University of Texas at Dallas

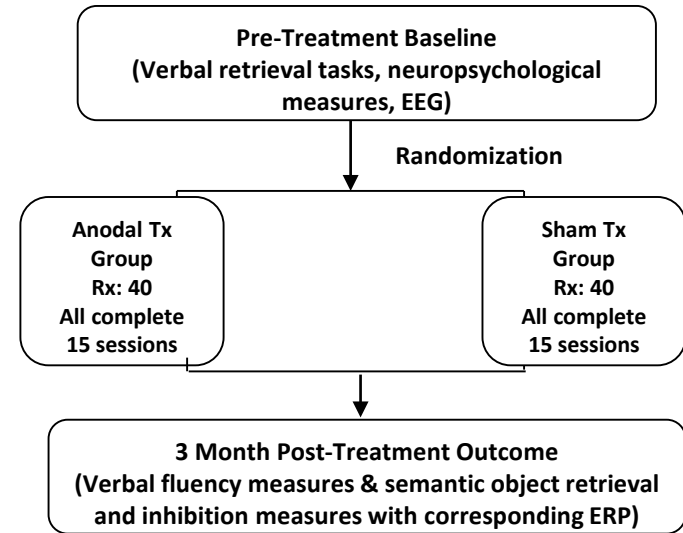
Award Amount: \$2,022,497

## Study/Product Aim(s)

- To extend a previous pilot and to measure response to treatment with 1 ma anodal HD tDCS over the preSMA region for a total of 15 sessions compared to sham stimulation. Follow-up assessments at immediate and 3 months post-treatment will be used for outcome response,
- Administer the Semantic Selection Go/NoGo and Semantic Object Retrieval tasks while measuring EEG at baseline, immediately after the 15<sup>th</sup> session, and at 3-months post-treatment to determine if there are behavioral and corresponding ERP changes secondary to the HD tDCS interventions.
- To develop an index based on concussion history and baseline neuropsychological battery scores to predict treatment response over the assessment periods.

## Approach

Veterans with TBI histories will be screened for verbal retrieval deficits to establish study eligibility. If they pass the screen, they will receive neuropsychological testing, a concussion history and semantic selection and object retrieval ERP tasks. If they then meet inclusion criteria, veterans will be randomly assigned to two treatment groups,-- active anodal HD tDCS or sham control, on a 1:1 basis. Each group receives 15 sessions. Follow-up testing will be performed at 3 month for outcome measure assessment.



Activities	Yr	2021	2022	2023
1. Screen 130 veterans for TBI and verbal retrieval deficits.		[Blue bar spanning 2021, 2022, and 2023]		
2. Acquiring pre-treatment neuropsychological baselines on 80 subjects		[Blue bar spanning 2021, 2022, and 2023]		
3. Acquiring pre-treatment EEG on 80 subjects		[Blue bar spanning 2021, 2022, and 2023]		
4. Treatment of 60 enrolled veterans		[Blue bar spanning 2021, 2022, and 2023]		
5. Acquiring post-treatment measures on projected number of 60 subjects completing the study		[Blue bar spanning 2021, 2022, and 2023]		
6. Analyzing data and disseminating findings				[Blue bar in 2023]
<b>Estimated Budget (\$K)</b>		\$750K	\$630K	\$642K

## Goals/Milestones

**CY 20 Goal** – Approval of regulatory documents

**CY 21-23 Goal** – Enrolling 80 subjects in the study

**CY 21-23 Goal** – Treatment and data collection

**CY 23 Goals** – Final analyses of data

## Comments/Challenges/Issues/Concerns

Continuing recruitment and enrollment of subjects; investing resources in recruiting existing patients to return for follow-up evaluations.

## Budget Expenditure to date

Projected Expenditure: \$ 749,935

Actual Expenditure: \$ 262,621

**Updated:** 23 September 2021