

AWARD NUMBER: W81XWH-20-1-0493

TITLE: High-Definition Transcranial Direct Current Stimulation in Episode Memory in Individuals with Amnesic Mild Cognitive Impairment and History of TBI

PRINCIPAL INVESTIGATOR: Dr. Christian LoBue, Ph

CONTRACTING ORGANIZATION: UT Southwestern Medical Center, Dallas, TX

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13. SUPPLEMENTARY NOTES					
14. ABSTRACT: Traumatic brain injury (TBI) is a risk factor for earlier development of Alzheimer dementia (AD), and amnesic mild cognitive impairment (aMCI) is often a prodromal stage for AD, representing the earliest clinical threshold where episodic memory deficits manifest. 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 from our group have demonstrated that the memory circuitry appears amenable to HD-tDCS modulation of the preSMA/dACC, with significant improvement in episodic memory seen in patients with a history of TBI. However, there is an absence of studies examining the efficacy of HD-tDCS to improve episodic memory in individuals with aMCI and a history of TBI. Research Strategy: To address this, the proposed project would be the first to assess whether HD-tDCS can improve episodic memory in aMCI individuals with a history of TBI. This will be a randomized, blinded study with two arms of intervention (active HD-tDCS stimulation or sham condition). A total of 24 former military and non-military participants with aMCI and a history of TBI will be randomized into the two intervention conditions based on a 2:1 ratio (Active n=16 versus Sham n=8). Participants will receive 10 sessions of either active HD-tDCS stimulation to the preSMA/dACC or sham across 2 weeks. A neuropsychological test battery consisting of episodic memory measures will be completed at baseline, immediately following session 10, and at a 3-month follow-up.					
15. SUBJECT TERMS None listed.					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 10	19a. NAME OF RESPONSIBLE PERSON USAMRDC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)

TABLE OF CONTENTS

	<u>Page</u>
1. Accomplishments	4
2. Products	8
3. Participants & Other Collaborating Organizations	8
4. Changes/Problems	10
5. Special Reporting Requirements	10

1. Accomplishments:

What were the major goals of the project?

This proposal seeks to determine the effect of HD-tDCS on improving episodic memory in individuals with aMCI and a history of TBI. The 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 either active stimulation (1 mA anodal HD-tDCS targeting preSMA/dACC for 20 min) or sham. Episodic memory tasks will be completed at baseline, immediately following session 10, and a 3-month follow-up.

What was accomplished under these goals?

- 1) During the second year, thirteen participants were enrolled and completed or initiated the protocol for treatment sessions. Currently, seven participants are awaiting their 3 month follow-up. Sources for potential participants have increased, with new clinics being advised of our study and contributing potential participants to be contacted for research opportunities.
- 2) The REDCap database instruments have been refined and proven to be a highly useful and flexible tool for data collection and report running.
- 3) Preliminary data were analyzed once 11 participants had completed HD-tDCS sessions. HD-tDCS targeting the dACC showed no direct benefit for episodic memory deficits in aMCI based on preliminary results. However, significant improvement in language and executive function skills occurred in response to HD-tDCS. Multiple participants in the active group had clinically significant enhancement in language and executive functioning tests, while nobody in the sham group did. Results suggest HD-tDCS in this configuration may have promising potential as an intervention for language and executive function deficits in MCI and we will further examine this once our enrollment goal has been achieved.
- 4) There have been a wealth of individuals willing to participate in research activities, however the team feels that the waves for the COVID-19 pandemic early in the year played a role in lowering overall recruiting rates with people being hesitant to participate in close quarters in-person research. The team feels that currently the enrollment chances are higher, reflecting a downtick in the COVID-19 pandemic, and is evidenced by us enrolling 6 participants between 3/2022 and 8/2022.

Describe the Regulatory Protocol and Activity Status (if applicable).

Describe the Protocol and Activity Status for sections a-c, as applicable, using the format described for each section. If there is nothing significant to report during this reporting period, state "Nothing to Report."

(a) Human Use Regulatory Protocols

TOTAL PROTOCOLS: One human subject research protocol will be required to complete the Statement of Work.

PROTOCOL(S): List the identifier and title for all human use protocols needed to complete the project. Include information about the approved target number for clinical significance, type of submission, type of approval with associated dates, and performance status.

The following format shall be used:

Protocol (of total):

Protocol [HRPO Assigned Number]:

Title:

Target required for clinical significance:

Target approved for clinical significance:

Submitted to and Approved by:

Provide bullet point list of protocol development, submission, amendments, and approvals (include IRB in addition to HRPO).

Status:

Report (i) progress on subject recruitment, screening, enrollment, completion, and numbers of each compared to original planned target(s), e.g., number of subjects enrolled versus total number proposed; (ii) amendments submitted to the IRB and USAMRMC HRPO for review; and (iii) any adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation.

TOTAL PROTOCOLS: 1

PROTOCOL (1 of 1 total):

Protocol [HRPO Assigned Number]: STU2019-1769

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

Target required for clinical significance: 24

Target approved for clinical significance: 24

SUBMITTED TO AND APPROVED BY:

- Study creation in eIRB Status: N/A Date: 12/19/19
- Study submission to IRB Status: Submitted Date: 3/11/20
- Study approved by department Status: Approved Date: 3/12/20
- HRPP changes requested Status: N/A Date: 3/17/20
- Protocol, consent, HIPAA documents requested clarification. These were submitted the same day as received.
- HRPP/IRB changes reviewed Status: Approved Date: 3/30/20
- Study modification (administrative change) Status: Approved Date: 6/17/20
- Study modification (administrative change and consent update) Status: Approved Date: 9/2/20
- Study modification (electronic consent method, addition of recruitment material, REDCap database language addition, administrative change) Status: Approved Date: 11/2/20
- Study modification (consent clarification, protocol clarification of device being used, elaboration of the team's experience using the device) Status: Approved Date: 3/5/21
- Continuing Review Status: Approved Date: 3/18/21
- Study modification (clerical updates regarding award number in IRB system) Status: Approved Date: 3/5/21

<ul style="list-style-type: none"> • Study modification (addition of supplemental recruitment site) Status: Approved Date: 12/14/21 • Continuing Review Status: Approved Date: 3/7/22 • Study modification (updated recruitment flyer and added recruitment letter) Status: Approved Date: 4/20/22 • Study modification (updated recruitment flyer) Status: Approved Date: 6/10/22 • Study modification (updated recruitment flyer contact information) Status: Approved Date: 7/15/22 <p><u>STATUS:</u></p> <p>(i) Number of subjects recruited/original planned target: 14/24 Number of subjects screened/original planned target: 42/30 Number of patients enrolled/original planned target: 14/24 Number of patients completed/original planned target: 7/24</p> <p>(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review:</p> <ul style="list-style-type: none"> • Study modification (addition of supplemental recruitment site) Status: Approved Date: 12/14/21 • Continuing Review Status: Approved Date: 3/7/22 • Study modification (updated recruitment flyer and added recruitment letter) Status: Approved Date: 4/20/22 • Study modification (updated recruitment flyer) Status: Approved Date: 6/10/22 • Study modification (updated recruitment flyer contact information) Status: Approved Date: 7/15/22 <p>(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: Nothing to report. All participants have tolerated HD-tDCS procedures well.</p>

**(b) Use of Human Cadavers for Research Development Test & Evaluation (RDT&E),
Education or Training**

“Cadaver” is defined as a deceased person or portion thereof, and is synonymous with the terms “human cadaver” and “post-mortem human subject” or “PMHS.” The term includes organs, tissues, eyes, bones, arteries or other specimens obtained from an individual upon or after death. The term “cadaver” does not include portions of an individual person, such as organs, tissue or blood, that were removed while the individual was alive (for example, if a living person donated tissue for use in future research protocols, that tissue is not considered a “cadaver” under this policy, regardless of whether the donor is living or deceased at the time of tissue use).

TOTAL ACTIVITIES: State the total number of RDT&E, education or training activities that will involve cadavers. If not applicable, write “No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW).”

ACTIVITIES: Provide the following information in a bulleted list for all RDT&E, education or training activities involving human cadavers conducted or supported during the quarter:

- Title of the RDT&E, education or training activity
- SOW task/aim associated with the activity
- Date the activity was conducted
- Identification of the organization’s responsible individual (e.g., PI or individual primarily responsible for the activity’s conduct)
- Brief description of the use(s) of cadavers in the activity and the total number of cadavers used during the reporting period
- Brief description of the Department of Army organization’s involvement in the activity
- Status of document submission and approvals
- Problems encountered in the procurement, inventory, use, storage, transfer, transportation and disposition of cadavers used for RDT&E, education or training. Examples of problems include but are not limited to: loss of confidentiality of cadaveric donors, breach of security, significant deviation from the approved protocol, failure to comply with state laws and/or institutional policies and public relations issues.

TOTAL ACTIVITIES: No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW).

(c) Animal Use Regulatory Protocols

TOTAL PROTOCOL(S):

State the total number of animal use protocols required to complete this project (e.g., 2 animal use research protocols will be required to complete the Statement of Work.). If not applicable, write “No animal use research will be performed to complete the Statement of Work.”

PROTOCOL(S):

List the identifier and title for all animal use protocols needed to complete the project. Include information about the approved target number for statistical significance, type of submission, type of approval with associated dates, and performance status.

The following format shall be used:

Protocol (of total):

Protocol [ACURO Assigned Number]:

Title:

Target required for statistical significance:

Target approved for statistical significance:

Submitted to and Approved by:

Status:

TOTAL PROTOCOL(S): No animal use research will be performed to complete the Statement of Work.

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

- Continue to meet with referring providers and send weekly email reminders about overall recruitment goals for each quarter and progress being made
- Continue to screen, recruit, and consent participants using electronic consent framework.
- Continue to complete neuropsychological assessments and HD-tDCS procedures with participants and pending 3-month follow-ups.
- Expand recruitment sources to other well-established clinics within the network. A meeting has been scheduled for late September to discuss a new collaboration

2. Products: List any products resulting from the project during the reporting period. If there are no products to report for the current quarter, state "Nothing to report."

Examples of products include:

- *publications, conference papers, and presentations;*
- *website(s) or other Internet site(s);*
- *technologies or techniques;*
- *inventions, patent applications, and/or licenses; and*
- *other products, such as data or databases, biospecimen collections, germplasm, audio or video products, software, models, educational aids or curricula, instruments or equipment, data and research material, clinical or educational interventions, or new business creation.*

A conference presentation from the project's preliminary results was submitted to the International Neuropsychological Society. The status of its acceptance is currently pending.

3. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name: Christian LoBue
Project Role: PI
Researcher Identifier (e.g. ORCID ID): 0000-0001-9671-5526
Nearest person month worked: 12
Contribution to Project: No change.

Name: Nyaz Didehbandi
Project Role: Co-I
Researcher Identifier (e.g. ORCID ID): 0000-0001-6121-5759
Nearest person month worked: 12
Contribution to Project: No change.

Name: Cason Hicks
Project Role: Lead Research Coordinator
Researcher Identifier (e.g. ORCID ID): 0000-0002-0175-1637
Nearest person month worked: 12
Contribution to Project: No change.

Name: Sarah Sprinkle
Project Role: Lead Administrative Contact
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 5
Contribution to Project: No change.

Name: Jessica Helpfrey
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): 0000-0001-5626-8055
Nearest person month worked: 8
Contribution to Project: No change.

Name: John Hart
Project Role: Collaborator
Researcher Identifier (e.g. ORCID ID): 0000-0003-3919-8125
Nearest person month worked: 4
Contribution to Project: No change.

Name: C. Munro Cullum
Project Role: Collaborator
Researcher Identifier (e.g. ORCID ID): 0000-0001-9706-5465
Nearest person month worked: 4
Contribution to Project: No change.

Name: Jan Garcia
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 5
Contribution to Project: No change.

Name: Michael Conley
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 8
Contribution to Project: No change.

<i>Name:</i>	<i>Hannah Doggett</i>
<i>Project Role:</i>	<i>Research Coordinator</i>
<i>Researcher Identifier (e.g. ORCID ID):</i>	<i>0000-0002-9006-8978</i>
<i>Nearest person month worked:</i>	<i>12</i>
<i>Contribution to Project:</i>	<i>No change.</i>

4. Changes/Problems:

a. Actual Problems or delays and actions to resolve them

The omicron variant of COVID-19 created an issue for even those participants that are typically willing to contribute to this body of research. Recruitment/enrollment was limited as a result of this early this year. Each participant is still screened for exposure before each visit to the research site, and masking is enforced at all times. In the last 6 months, though, recruitment has greatly increased as we were able to recruit 6 individuals during this timeframe and have more scheduled.

We previously increased the breadth of our screening with the addition of referral clinics in our network. This action has opened up the amount of potential participants available, therefore increasing our enrollment going in year 2. We will continue to seek other access points within our network to increase enrollment, and have a meeting with a potential new referral site scheduled for later this month. If successful, we believe this collaboration could send many more referrals to greatly improve our recruitment.

b. Anticipated Problems/Issues

We anticipated the omicron variant of COVID-19 to cause recruitment problems early this year. Recently, there has been a noticeable increase in enrollment. We attribute this to the decrease in COVID cases as well as an increase in our research network. With the upcoming holidays, participants may be reluctant to complete the 10 sessions of HD-tDCS on a week that involves a major holiday. We are attempting to enroll the maximum number of participants possible on weeks that do not overlap these, and during the holiday weeks, research members will use the time to be present in some referral clinics to boost possible recruitment for after the holiday.

5. Special Reporting Requirements:

Quad Charts: Attached.