AWARD NUMBER: W81XWH-20-1-0493

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

PRINCIPAL INVESTIGATOR: Dr. Christian LoBue, Ph

CONTRACTING ORGANIZATION: University of Texas, Southwestern Medical Center
Dallas, TX

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

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6. AUTHOR(S)

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E-Mail:

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Texas, Southwestern Medical Center
5323 Harry Hines Blvd, Dallas, TX 76093

8. PERFORMING ORGANIZATION REPORT NUMBER

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U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

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12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT:

Traumatic brain injury (TBI) is a risk factor for earlier development of Alzheimer dementia (AD), and amnestic 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 circuity 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**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRDC
U	U	U	UU	12	**19b. TELEPHONE NUMBER** *(include area code)*

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Accomplishments: The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project identify these dates and show actual completion dates or the percentage of completion.

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 active stimulation (1 mA anodal HD-tDCS targeting preSMA/dACC for 20 min) or sham. Episodic memory tasks will be completed at baseline, immediate follow-up after session 10, and a 3-month follow-up.

Aim. Determine the effect of HD-tDCS on episodic memory in patients with aMCI and a history of TBI.

Hypothesis. 1 ma anodal HD-tDCS to the preSMA/dACC will result in improvements in episodic memory tasks over the sham condition, while no significant improvement results for the sham condition across follow-up assessments.

<u>Pre-Study Tasks:</u>

Task 1. Months 1-6.	
Obtain Institutional Review Board (IRB) Protocol Review and Approval	Completed 03/25/2020
Obtain ORP/HRPO Approval	Completed 09/01/2020
Task 2. Months 1-6.	
Set up HD-tDCS administration protocols	Completed 11/15/2020
Set up laboratory space for administration of neuropsychological battery	Completed 11/15/2020
Task 3. Months 1-6.	
Recruit and train staff in HD-tDCS and neuropsychological procedures	Completed 11/15/2020

<u>Study Tasks:</u>

Task 1. Months 1-30.	
Recruitment and scheduling of participants with aMCI and a history of TBI	In Progress, 92% Complete
Task 2. Months 1-30.	
Administration of HD-tDCS and outcome measures	In Progress, 86% Complete
Task 3. Months 24-36.	
Statistical analyses to address proposal's Aim/Hypothesis	Pending
Task 4. Months 30-36.	
Write up and submit manuscripts	Pending
Task 5. Months 36.	
Prepare and submit final report	Pending, One-Year No-Cost Extension to 8/31/2024

What was accomplished under these goals?
For this quarterly reporting period only describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided.

Study Tasks:
Task 1. Recruitment and scheduling of participants with aMCI and a history of TBI
a) During the third year, a total of 19 participants were enrolled and completed or initiated the protocol for treatment sessions. As of the time of this report, 3 additional participants have been enrolled, of which 2 have completed treatment sessions, and 1 initiated treatments.

b) We did not meet our target sample of 24 subjects, but we are nearing completion with 22/24 participants at present. Referrals for potential participants decreased during the latter part of the year, despite continued collaborative efforts with clinics.

c) New clinics, such as Parkland Health and the North Texas VA, have been incorporated as recruitment sites for the study and have been trying to refer potential participants to be contacted for research opportunities.

3) Community outreach and engagement has been a major activity. We provided 3 educational talks to the community and living facilities about brain health, MCI/ADRD, current treatments, and our available clinical trial. This has created significant interest, and while many people have wanted to participate in the study, they have not met the eligibility criteria in that many lack a diagnosis of amnestic MCI.

Task 2. Administration of HD-tDCS and outcome measures
HD-tDCS treatments and all outcome measures have been completed for 19 participants. One participant is currently being administered HD-tDCS treatments. A total of three participants are currently awaiting their 3 month follow-up visit and these have been scheduled.

Task 3. Statistical analyses to address proposal's Aim/Hypothesis
Preliminary data was presented at the annual conference for the International Neuropsychological Society in 02/2023.

At the time of submission for the conference, 11 participants with aMCI had completed the study and had the data in our electronic data management system checked for quality assurance. This consisted of 7 participants who were randomized to receive 1 mA HD-tDCS and 4 randomized to receive sham stimulation. Table 1 below provides a summary of the participant characteristics.

Composite scores for memory and non-memory (language + executive function) tests were derived.

Changes in composite scores were compared among groups and the frequency of participants with clinically significant change, defined as > 1 SD improvement on at least one test for the memory and non-memory domains, was also compared. Table 2 contains the composite scores as well as scores for each test measure for the groups receiving 1 mA HD-tDCS and sham stimulation.

In this preliminary analysis, episodic memory scores did not show statistical or clinically significant differences from baseline for the 1mA HD-tDCS group.

Interestingly, the language/executive function composite score (non-memory abilities) showed statistically significant improvement only for the 1mA HD-tDCS group ($p = 0.04$).

Also, multiple participants in the 1mA HD-tDCS group ($n = 3$) had clinically meaningful improvement on the language/executive function composite ($p = 0.07$), while none in the sham group did.

Table 1
Demographics and Clinical Data of Participants

	Active HD-tDCS *(n = 7)*	**Sham Stimulation** *(n = 4)*
# Single Domain aMCI	2	1
# Multidomain aMCI	5	3
# Female/Male	1 / 6	2 / 2
# White Racial Background	7	4
Age, *M (SD)*	69.57 (7.46)	73.25 (7.23)
Timing of Diagnosis, *M (SD)*	2.20 yrs prior (1.64)	2.33 yrs prior (1.15)
Education, *M (SD)*	16.57 (1.90)	17.5 (1.91)
AMNART Estimated Premorbid Ability *M (SD)*	114.69 (11.48)	122.50 (3.70)

Table 2
Neuropsychological Test Scores

	Active HD-tDCS M (SD)		**Sham Stimulation M (SD)**	
	Initial	Post-treatment	Initial	Post-treatment
Memory Composite Score	123.43 (37.42)	120.29 (35.35)	135.00 (28.67)	133.25 (25.55)
HVLT-R Total Learning	34.29 (9.27)	33.29 (10.78)	37.75 (8.06)	35.00 (2.31)
HVLT-R Delayed Recall	25.71 (10.24)	25.57 (12.23)	27.75 (13.57)	31.25 (8.96)
BVMT-R Total Learning	31.57 (11.96)	29.86 (8.75)	33.25 (11.18)	34.50 (9.61)
BVMT-R Delayed Recall	31.86 (12.12)	31.57 (9.48)	36.25 (12.50)	32.50 (10.66)
Language/Executive Function Composite Score	123.15 (39.94)	138.43 (33.21)	127.50 (37.30)	133.25 (46.80)
Semantic Fluency	43.29 (18.36)	48.71 (15.52)	36.50 (16.18)	38.00 (20.54)
Trail Making Test B	41.00 (18.07)	48.71 (13.21)	48.00 (12.33)	52.25 (16.96)
Stroop Color-Word Trial	38.86 (8.78)	41.01 (11.12)	43.00 (12.03)	43.00 (11.20)

Note. Individual test scores are t-scores

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 Amnestic 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
- 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

STATUS:

(i) Number of subjects recruited/original planned target: 22/24
Number of subjects screened/original planned target: 85/30
Number of patients enrolled/original planned target: 22/24
Number of patients completed/original planned target: 19/24

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review:

- 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
- Study modification (Revision of the PHHS Recruitment Letter and revision of the Form C to include recruitment process that includes ClinDEN query system)
  Status: Approved Date: 10/17/22
- Study modification (Updating contact information on both study flyer and consent form as well as updating personnel form B)
  Status: Approved Date: 1/03/23
- Study modification (Updating phone number on recruitment flyer and consent form. Also in consent form under PHI, changing the way we code participant's research IDs.)
  Status: Approved Date: 2/16/23
- Removed unnecessary spaces between words, added commas where necessary, changed address phone number of Principle Investigator due to office change. Changed 'e-consent' in footer to 'consent' since we are only doing in-person consents.)
  Status: Approved Date: 3/10/23
- Study modification (Modification 14 removed the e-consent option from the Form C and the consent form, but it was inadvertently left in the protocol.)

Status: Approved Date: 3/20/23

- Study Modification 15 (transitioned from digital consenting to in person consenting only)
  Status: Approved Date: 3/20/23

(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.

(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:

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

Status:

Provide bullet point list of performance and/or progress status relating to the above protocol and discuss any administrative, technical, or logistical issues that may impact performance or progress of the study (e.g. animal use protocol needs revision to minimize animal suffering, animal protocol modification to include additional staff) for the above ACURO approved protocol.

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?

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

- Continue to meet with referring providers face-to-face and send weekly email reminders about overall recruitment and progress being made
- Continue to engage in community outreach and engagement
- Optimize collaborations with new referral clinics to accomplish our recruitment goals
- We will continue having a study team member attend clinic sites to interact with clinical providers and facilitate receiving more referrals
- Continue to screen, recruit, and consent participants
- Continue to complete HD-tDCS procedures and neuropsychological assessments with participants and the pending 3-month follow-ups
- Continue to perform data quality checks of the electronic data management system to allow us to quickly perform data analyses to complete Task 3 (statistical analyses) and begin Task 4 (Preparation of manuscripts)

1. 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."

A conference paper and presentation resulted from a preliminary analysis of results. The presentation was at the annual conference for the International Neuropsychological Society in 02/2023 and the paper proceeding was published in the Journal of International Neuropsychological Society. Citation below.

LoBue, C., Didehbani, N., Chiang, H-S., Hart, J., Helphrey, J., Conley, M., Smernoff, E., Lacritz, L., Reese, C., Cullum, C.M., Marshall, C., Nguyen, T., Kelley, B., Khera, A., Frolov, A., Martinez, N., Logan, R. (2023). Preliminary evidence of a therapeutic effect of electrical neuromodulation on cognitive deficits in patients with Mild Cognitive Impairment. *Journal of the International Neuropsychological Society.* Supplemental Issue 2

2. Participants & Other Collaborating Organizations

What individuals have worked on the project?
Provide the following information for: (1) Project Directors (PDs)/ PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort).

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 Didehbani*
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: *Danyah Ahmed*
Project Role: *Lead Research Coordinator*
Researcher Identifier (e.g. ORCID ID): 0000-0003-4255-8216
Nearest person month worked: *9*
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 Helphrey*
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.*

3. Changes/Problems: The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

a. Actual Problems or delays and actions to resolve them

Provide a description of current problems or issues that may impede performance or progress of this project along with proposed corrective action. Also describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

For an award that includes the recruitment of human subjects for clinical research or a clinical trial, discuss any problems or barriers encountered, if applicable, and what has been done to mitigate those issues. Discussion may highlight enrollment problems, retention problems, and actions taken to increase enrollment and/or improve retention.

Time limitations for participation remains a barrier for enrollment with some recent referrals given these persons are employed and cannot take time off for participation. Also, referrals from clinical providers decreased during the latter half of the year, despite us having a presence in the clinics and regular communication with providers. In talking with the providers, aMCI patients are being considered for the new antibody drug (lecanumab), which corresponds with the reduced referrals. However, the procedures required to establish candidacy and safety for this drug takes ~3 months at our institution. Thus, clinical providers were informed that aMCI patients who wish to receive the drug could be referred to this study and complete all procedures prior to initiating lecanumab.
To offset the other challenge related to time limitations, we began community outreach activities to boost screening and enrollment for the study. We also increased the number of available recruitment sites to involve Parkland Health and the North Texas VA.

b. Anticipated Problems/Issues

Provide a description of anticipated problems or issues that have a potential to impede performance or progress. Also provide course of actions planned to mitigate problems or to take should the problem materialize.

With the unexpected reduction in referrals from clinics, we did not enroll the maximum number of patients for the trial. However, we have identified the source of reduced referrals being largely due to aMCI patients going through workups to establish candidacy and safety for taking lecanumab. Discussions with clinical providers about our capability to enroll patients interested in our study and have them finish all procedures before starting lecanumab should enhance our referrals. Indeed, we have recruited 3 additional participants since that time. We requested a 1-year NCE and received approval and we are focused on enrolling the final 2 participants to achieve our target enrollment numbers.

4. Special Reporting Requirements:

Quad Charts: Attached.