AWARD NUMBER: W81XWH-17-1-0432

TITLE: High-Definition Transcranial Direct Current Stimulation (HD-tDCS) for Sensory Deficits in Complex Traumatic Brain Injury

PRINCIPAL INVESTIGATOR: Davin Quinn, MD

CONTRACTING ORGANIZATION: University of New Mexico Health Sciences Center

REPORT DATE: OCTOBER 2021

TYPE OF REPORT: Annual Technical Progress Report

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
OCTOBER 2021	Annual Report	30SEPT2020 - 29SEPT2021

4. TITLE AND SUBTITLE

High-Definition Transcranial Direct Current Stimulation (HD-tDCS) for Sensory Deficits in Complex Traumatic Brain Injury

5a. CONTRACT NUMBER
W81XWH-17-1-0432

5b. GRANT NUMBER
PT160096

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Davin Quinn, MD

E-Mail: dquinn@ salud.unm.edu

5d. PROJECT NUMBER
0011055720–0006

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

University of New Mexico Health
Sciences Center
MSC09 5030
1 University of New Mexico
Albuquerque, NM 87131

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The purpose of this research is to use high-definition transcranial direct current stimulation (HD-tDCS) to treat neurosensory postconcussive symptoms (PCS) associated with mild traumatic brain injury (mTBI) in US Veterans and Warfighters. A randomized sham-controlled clinical trial will be performed. We will recruit 120 participants ages 18-59 for the study: 80 participants with mTBI to undergo the intervention, and 40 non-TBI healthy subjects to act as an imaging-only control group. The intervention is 10 days of anodal HD-tDCS to the left dorsolateral prefrontal cortex, paired with vision therapy and cognitive training. Magnetic source imaging (MSI), neuropsychological assessment, and neurosensory evaluation, are obtained before and after the intervention, to assess changes in brain function, postconcussive symptom burden, and quality of life. During this reporting period, preliminary data has been generated demontrating improvements in neurosensory function, cognitive control, and brain activation patterns with the intervention.

15. SUBJECT TERMS
Traumatic brain injury; postconcussive symptoms; neurosensory; transcranial direct current stimulation

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRDC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)*
U	U	U	UU	26	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1. Introduction

The purpose of this research is to use high-definition transcranial direct current stimulation (HD-tDCS) to treat neurosensory postconcussive symptoms (PCS) associated with mild traumatic brain injury (mTBI) in US Veterans and Warfighters. A randomized sham-controlled clinical trial will be performed. We will recruit 120 participants ages 18-59 for the study: 80 participants with mTBI to undergo the intervention, and 40 non-TBI healthy subjects to act as an imaging-only control group. The intervention is 10 days of anodal HD-tDCS to the left dorsolateral prefrontal cortex, paired with virtual reality-based and computer-based sensory training. Magnetic source imaging (MSI), neuropsychological assessment, and neurosensory evaluation, are obtained before and after the intervention, to assess changes in brain function, postconcussive symptom burden, and quality of life. The specific aims are to (1) assess the efficacy of excitatory HD-tDCS combined with sensory training tasks to improve subjective neurosensory postconcussive symptoms, objective cognitive control, and quality of life in veterans and warfighters with mTBI relative to training tasks alone and (2) characterize aberrant neuromagnetic activation in cognitive control networks in complex mTBI and identify network responses to targeted brain stimulation.

2. Keywords

High-Definition Transcranial Direct Current Stimulation (HD-tDCS), traumatic brain injury (TBI), sensory deficits, veterans, Magnetic Source Imaging (MSI), post-concussive, neurosensory, prefrontal cortex, cognitive control, quality of life, brain stimulation.

3. Accomplishments:

3.1 Accomplishments:

What were the major goals of the project?

	Timeline (Months)	% Complete	Completion Date
Major Task 1: Prepare protocol for brain stimulation and training			
Subtask 1: Prepare Regulatory Documents and Research Protocol			
If Applicable, coordinate with Sites for CRADA submission, clinical trial agreements (CTAs) submission, nondisclosure agreements *Data transfer agreements are complete with all contributing consultant sites.*	1-3	100%	02/2018
Finalize eligibility, exclusions, screening, consent, protocol *Eligibility and exclusion criteria, consent and protocol complete.*	1-3	100%	04/2018
Coordinate with Sites for UNM and VA IRB submission/review *Initial IRB approval from UNM obtained 11/23/2016. Initial IRB approval from VA obtained 11/16/2017. All other modification approvals are listed below:*	1-3	100%	**Initial UNM Approval** 11/23/2016 **Initial VA Approval** 11/16/2017

UNM -Updates to protocol, consent, recruitment processes, approved 10/04/2017 -Continuing Review, approved 11/06/2017 -Submitted modifications requested by the DoD Scientific Office, approved 02/21/2018 -Updates to assessments, approved 04/18/2018 -Adding and removing study team members, approved 06/06/2018 -Modifying assessments, updates to consent and protocol, approved 07/06/2018 -Receipt of Certificate of Confidentiality reported, acknowledged 08/06/2018 -Modified consent to reflect receipt of CoC, approved 08/31/2018 -Continuing Review, approved 09/12/2018 -Added assessment, adding study team member, updated consent, approved 10/26/2018 -Adding study team member, approved 11/07/2018 -Protocol updates & adding study team member, approved 06/07/2019 -Continuing review, approved 07/03/2019 -Protocol & consent updates, approved 01/09/2020 -Protocol, consent, and case report form updates, approved 03/09/2020 -Reportable New Information/ COVID-19 memo, acknowledged 03/26/2020 -Adding new study team member, 04/05/2020 - Continuing Review approval 06/03/20 **-**Study Safety updates to protocol, consent, adding forms approved 07/20/20 **-**Adding and removing study team members, approved 08/17/20 -Updated consent and protocol to allow for electronic merchandise cards for participant visits, approved 12/22/20 -Adding study team member, approved 02/08/21 -Continuing Review, approved 06/01/21 -Adding study team members, approved 06/14/21 **VA** -Adding study team member, 01/09/2018 -Submitted modifications requested by the DoD Scientific Office, approved 02/26/2018 -Consent and protocol updates, approved 05/11/2018 -Consent and protocol updates, approved 07/20/18 -Adding study team member, approved 08/13/2018 -Adding study team member, approved 09/24/2018 -Continuing Review, approved 10/09/2018 -Updated protocol to reflect use of 10 electrodes, updated recruitment flyer to be clear that we are also recruiting Healthy Controls, approved 01/17/2019 -Adding study team member, approved 02/21/2019 -Continuing Review, approved 10/10/2019 -Removing study team member, 01/09/2020 - Protocol, consent, and case report form updates, approved 02/27/2020 - COVID-19 memo, acknowledged, 03/19/2020 -Removing study team member, approved 08/17/20 -Continuing Review approved 09/16/20			

-Consent audit passed, 5/26/21 -Continuing review approved 09/02/21			
Coordinate with Sites for Military 2nd level IRB review (ORP/HRPO) *Received DoD approval to begin study on 05/18/2018. Annual reports completed in 2019 and 2020.*	1-6	100%	**Initial DoD Approval** 05/18/2018
Submit amendments, adverse events and protocol deviations as needed. *Reportable new information events submitted to UNM and VA, listed below. Note that "Reportable New Information" and "Event Determination" are synonymous language for reporting adverse events by UNM and VA respectively. All amendments and events submitted to UNM and VA IRB's have been submitted to DoD.* **Below includes adverse events and protocol deviations. All amendments listed in (a) Human Use Regulatory Protocols** - On 07/31/2019, M87111517 reported headache and vomited during neurosensory assessment. Submitted as RNI on 11/19/19 with intent to modify consent to indicate this as a risk with this assessment. Modification of consent in review with UNM IRB. - On 09/05/2019, M87103937 reported headache during neurosensory assessment, submitted as RNI on 11/19/19 with intent to modify consent to indicate this as a risk with this assessment. Modification of consent in review with UNM IRB. VA -On 11/22/2019, participant M87195559, reported having PTSD dreams the previous night, which he attributed to the stimulation. IRB determined: Event (isolated occurrence of PTSD-related dreams, not associated with subsequent treatment) was not serious, not anticipated, and not related to the research. No further action is required. No further reporting is required.	As needed	100%	Ongoing
Coordinate with Sites for annual IRB report for continuing review (CR): UNM -Continuing Review, approved 07/03/2019 -Continuing Review, approved 06/03/20 -Continuing Review, approved 06/01/21 VA -Continuing Review approved 10/10/19 -Consent audit passed 12/06/19 -Full study audit passed 06/29/20 -Continuing review approved 09/16/20 -Consent audit passed 05/27/21	Annually	100%	Ongoing

-Continuing review approved 09/02/21			
Major Task 2: Coordinate Study Staff and Resources for Clinical Trial			
***Subtask 1**: Hiring and Training of Study Staff*			
Coordinate with Sites for job descriptions, advertising, interviewing ***New study team member, Kevin Wilson and Jude Chavez, have been added to the study. They have trained in study protocol and completed required trainings at UNM. Research technician, Marcus Sterling, will be leaving study in January to pursue their education.***	1-8	100%	02/2018
Coordinate for space allocation for new staff *Space allocation finalized for UNM and VA, task complete.*	1-8	100%	01/2018
***Subtask 2**:*			
Coordinate with Sites for hiring, training Research Coordinator/Assistant, supervision, checks for 100% concordance *Coordinator and technicians have completed training in neuropsychological testing, brain stimulation, sensory evaluation, and neuroimaging. Now conducting periodic procedural fidelity checks.*	8-20	100%	07/2019
Procure and test imaging protocols, brain stimulation equipment and eye tracking devices, and create pipelines for data procurement and storage *Eye tracking devices tested and pilot data obtained and analyzed through data pipeline. MEG and MRI scan sequences and related tasks tested and pilot data obtained and analyzed through data pipeline. Electrical field modeling pipeline and electrode placement algorithm 100% complete. Brain stimulation equipment, tested, operating as expected.*	8-20	100%	07/2018
Major Task 3: Participant Recruitment, Brain Stimulation, Sensory Rehabilitation, Neuromagnetic Scanning, Participant Evaluation			
Subtask 1:			
Coordinate with Sites for flow chart for all study steps, web data collection and database requirements *Development of flow charts, Standard Operating Procedures for all protocol components, COINS data capture system, and data analysis tools complete.*	4-8	100%	04/2018
Finalize assessment measurements *Finalized assessments were submitted to the UNM and VA IRB for review and have been approved.*	1-4	100%	03/2018
Begin subject recruitment	8-36	33%	Ongoing

Recruitment activities that have taken place include: 1) flyer distribution to VA Polytrauma and Ambulatory Care Clinics; 2) information table staffed at VA Research Week and each month; 3) Polytrauma patients identified from registry and contacted, and recruitment letters mailed; 4) community veteran recruitment; 5) correspondence with UNM and VA clinicians for subject referrals.			
Participants complete testing and intervention over 3 weeks, N = 120 *# Potential subjects identified: 314* *# Screened by phone: 162 (55 HC, 107 TBI)* *# Enrolled: 63 (27 HC, 36 TBI)* *# Completed Visit 1: 63 (27 HC, 36 TBI)* *# Completed stimulation: 29 (29 TBI)* *# Completed Visit 2: 28 (28 TBI)*	8-36	39%	Ongoing
Complete follow-up assessments 1, 3, 6 months after completion of the brain stimulation treatment. *# Completed 1-month call: 30 (30 TBI)* *# Completed 3-month call: 30 (30 TBI)* *# Completed 6-month call: 29 (29 TBI)*	13-36	25%	Ongoing
Major Task 4: Data Analysis			
***Subtask 1**:*			
Report all analyses according to specifications, share output and finding with all investigators *Full analysis will be done once study data is obtained.*	36-48	0%	Ongoing
Work with data core and dissemination of findings (abstracts, presentation, publications, DOD) *Abstract of preliminary fMRI study data presented to Academy of Consultation-Liaison Psychiatry Annual Meeting (November 12-16, 2019).* *Abstract of preliminary iSCAN study data presented to Northeast Bioengineering Conference 2020* *Abstracts on neurosensory performance and fMRI/cognitive control data presented at MHRSR online August 26-27, 2020* ***Preliminary data on fMRI, eye tracking, and cognitive data presented to Academy of Consultation-Liaison Psychiatry Annual Meeting, November 10-12, 2021.*** ***Preliminary data on fMRI, eye tracking, and cognitive data presented to MOMRP FY21 Auditory, Vision, and Vestibular In Progress Review Meeting, July 20-21, 2021.***	36-48	50%	Ongoing
Upload data to FITBIR for data sharing *FITBIR compatibility of data storage complete. Upload will be done as study data is obtained.*	36-48	50%	Ongoing

Common Data Element and Unique Data Element assessment performed with FITBIR. Construction of upload pipeline with collaborators complete.			

3.1.1 ***Major Activities***

Our study team and PI for the project "HD-tDCS for Sensory Deficits in Complex Traumatic Brain Injury" have been productive with regards to Major Goals as outlined in the Statement of Work, although the COVID-19 pandemic has led to an unexpected but necessary pause in protocol enrollment.

The major activities accomplished of the study team and PI for the previous annual reporting period include the following:

(a) Regulatory: Continuing reviews by UNM IRB and VA IRB both completed successfully and submitted to DoD OHRP. Continuing review by DoD OHRP completed and approved.

(b) Administrative: A no-cost extension (NCE) for 1 year was requested by the study team and approved. Subawards have been edited and finalized for the NCE year. Investigator meetings now focus on pertinent study issues to successfully resume recruitment and protocol administration, i.e., COVID-19 precautions, recruitment strategies during COVID-19 pandemic, and preliminary data analysis.

(c) Personnel: New study staff, Kevin Wilson and Jude Chavez have been added to the team. They have completed necessary trainings and certifications to perform the study tasks, including CITI, HIPAA, and FCOI certifications, MRI and MEG performance and safety training, brain stimulation performance and safety training, oculomotor and neurosensory assessment, neuropsychological testing. All study staff have been trained and certified with regard to local, state, and CDC guidelines regarding COVID-19 precautions, including cleaning and disinfection of equipment before, during, and after study visits, use of personal protective equipment (PPE), social distancing measures, and screening procedures.

(d) Scientific: Currently 63 participants (27 Healthy Controls and 36 TBI) have been enrolled and 29 of the TBI participants completed the treatment as indicated. Abstracts were presented at the online 2020 MHSRS conference, and presentations of preliminary fMRI, eye tracking, and cognitive data were presented at the 2021 ACLP conference, and the MOMRP FY21 Auditory, Vision, and Vestibular IPR. Feedback was received from the review panel and has been incorporated into the study plan.

(e) Through research tables in the Albuquerque VA lobby, flyers, word of mouth, with Veteran support services and organizations, and seeking out online and social media organizations for Albuquerque Veterans and recruitment events, we are able to continue to enroll participants. Due to the pandemic and previous halt of study activities, we have not reached goals initially set at the beginning of this study. We have enrolled civilian healthy controls and TBI patients to bolster the number of participants given previous obstacles including loss of access to active-duty population.

Study recruitment, enrollment, and procedures take place with necessary and appropriate COVID-19 precautions in place to protect participants and staff.

3.2 Specific Objectives

The specific objectives of the study are:

Aim 1 (Symptom Reduction): To assess the efficacy of HD-tDCS combined with rehabilitation tasks to improve subjective postconcussive sensory symptoms, objective measures of cognitive control, and long-term quality of life in Veterans and Warfighters with complex TBI relative to rehabilitation training alone.

Aim 2 (Target Engagement): To characterize aberrant neuromagnetic activation in sensory and cognitive control networks in complex mTBI,and identify network responses to targeted brain stimulation.

3.3 Significant Results or Key Outcomes

We have also demonstrated differences in BOLD signal during working memory task performed while undergoing functional magnetic resonance imaging (fMRI) between healthy controls and TBI patients. While this is trending toward significance, we expect that with increased subjects we will be able to confirm this finding. It is consistent decreases in BOLD signal on functional magnetic resonance imaging from before intervention to after intervention. This corresponding with improved cognitive performance on a multimodal working memory task. See Figure 1.

3.3.1 Other Achievements

Nothing to report.

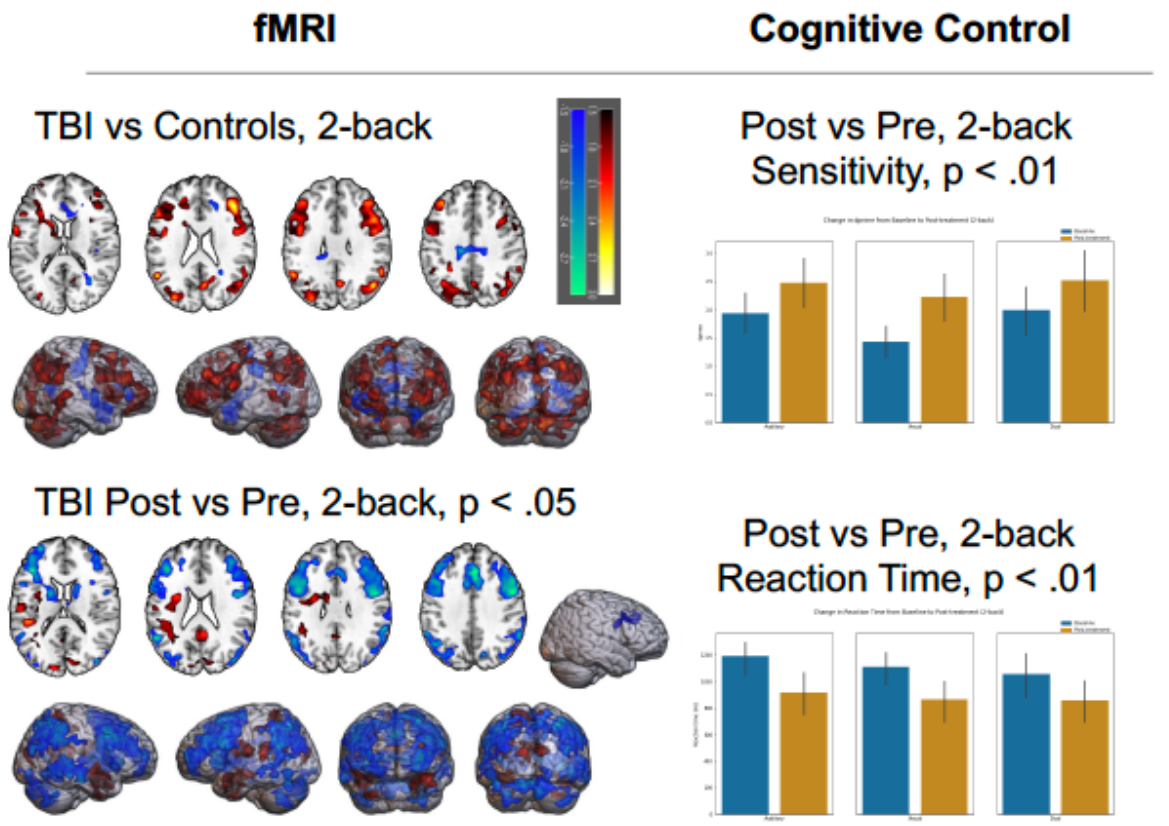

Figure 1. Top left: Difference in fMRI BOLD signal during performance of a multimodal 2-back task between healthy controls and TBI patients at baseline prior to intervention. Red = greater activation in TBI compared to controls. Blue = less activation in TBI compared to controls. Dorsolateral prefrontal and posterior parietal areas (I.e., cognitive control network; CCN) in TBI patients demonstrated greater activation, although this result was not significant. Bottom left: TBI patients then went on to receive virtual reality vision training sessions alternating with N-back training sessions for 10 consecutive days while receiving high-definition transcranial direct current stimulation. Differences in BOLD signal during multimodal 2-back task between TBI patients post-intervention and pre-intervention are displayed. Blue = less activation after intervention. Red = more activation after intervention. After correction for multiple comparisons, differences were significant in the area of the right prefrontal cortex, $p < .05$. N = 22 in each group. Right: cognitive performance in the TBI group demonstrated improvement from baseline to post-intervention in sensitivity (accuracy) and reaction time in auditory, visual, and dual targets, $p < .01$. Results suggest that TBI is associated with hyperactivation in CCN but improves with training, confirming the theory of cognitive inefficiency.

Stated Goals Not Met

To date, the only study goals not met at the time of this annual report are the stated recruitment goals: 120 TBI subjects and 40 healthy control subjects were anticipated to have been enrolled by end of Year 4, whereas the study has recruited 39 TBI subjects and 24 control subjects to date. This is attributable to several factors:

a) delays in full HRPO approval to begin the study, due to required necessary modifications to UNM and VA IRB protocols.
b) lack of an updated letter of support from the commanding officer of an identified Active Duty population, resulting in an inability to recruit this population.

c) slower than expected intake of potential patients into the NMVAHCS Polytrauma Support Clinic.
d) pandemic closures preventing recruitment and enroll participants for 6 months.

Please see next section for description of efforts to meet this goal.

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

Nothing to report.

3.5 How were the results disseminated to communities of interest?

Nothing to report.

3.6 Planning

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

With approval of the no-cost extension, the study team will have an additional year to continue recruitment, enroll subjects, obtain data, and analyse it to achieve the study aims. We will continue the strategies for recruitment that have met with the most success, including holding research tables in the VA lobby, Polytrauma referrals, posting advertisements on social media and websites, and word of mouth.

With regard to data analysis, to date we have processed and performed preliminary analysis of neurosensory, eyetracking, cognitive, and fMRI data. In this next reporting period we will turn our focus to the magnetoencephalography (MEG) data, which study team member Dr. Julia Stephen is now processing, as Director of the MEG Core at Mind Research Network. This will be the last data stream that we will prepare for interpretation when unblinding of the stimulation condition will occur.

4. Impact

4.1 What was the impact on the development of the principal discipline of the project?

The study team has demonstrated that the common aspects of the intervention, ie. the virtual reality vision training and the cognitive training, have objective, significant beneficial effects on convergence/divergence eye movements, working memory performance, and brain activation. After the intervention, TBI participants are closer in the above domains to healthy control participants' levels of performance. While there is no arm of the study that controls for spontaneous recovery without intervention, we believe that the results are strong enough to warrant a separate study that looks at the virtual reality vision training as a sole intervention, with more sessions over a longer period of time, to maximize the potential improvement to be gained.

4.2 What was the impact on other disciplines?

Nothing to report at this time.

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

Nothing to report at this time.

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

The eventual completion of this study, engaging the main academic medical centers in the Albuquerque metropolitan area, has the potential to raise the awareness of military TBI in the Southwest region, and to encourage further study of, advocacy for, and funding of interventions that will help improve the lives of Veterans and Warfighters living with TBI.

It also will shift the prevailing train of thought regarding postconcussive symptoms and their etiology. Currently, these are viewed as largely driven by psychological states, such as anxiety, stress, and depression. Our study shows a true difference in the neurosensory functioning of the brain after mTBI, which will move paradigms of treatment toward physiologically oriented therapies.

5. Changes/Problems

5.1 ***Changes in approach and reasons for change***

None at this time. We will continue recruiting civilian controls and TBI patients in order to offset recruitment deficits stemming from inability to recruit active-duty personnel.

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

a) COVID-19 pandemic restrictions: While the study is currently operating without restriction, it is not known whether future pandemic-related state, federal, or institutional restrictions may be put into effect, given ongoing concerns about variant strains and altered infectivity.

b) COVID-19 precautions: All protective measures for COVID-19 have been instituted, including use of protective equipment, social distancing, and cleaning procedures.

c) Recruitment Lag: A no-cost extension has been approved and will allow the study team to continue recruitment for an additional year.

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

Nothing to report. The no-cost extension will not alter the study total budget.

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

Nothing to report.

Human Use Regulatory Protocols
TOTAL PROTOCOLS: 2

PROTOCOL (1 of 2 total):

Protocol [UNM HRPO Assigned Number]: 16-376

Title: High-Definition Transcranial Direct Current Stimulation for Sensory Deficits in Complex Traumatic Brain Injury

Target required for clinical significance: 120

Target approved for clinical significance: 120

Submitted to and approved by: University of New Mexico Health Sciences Center Human Research Review Committee, Human Research Protections Office

-Initial approval 11/23/2016

Status: Recruitment commenced June 2018

(i) Recruitment

-Number of subjects recruited/original planned target: 314/1000
-Number of subjects screened/original planned target: 162400
-Number of patients enrolled/original planned target: 63/120
-Number of patients completed/original planned target: 55/120 (27 HC, 28 TBI)

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

-Updates to protocol, consent, recruitment processes, approved 10/04/2017
-Continuing Review, approved 11/06/2017
-Submitted modifications requested by the DoD Scientific Office, approved 02/21/2018
-Updates to assessments, approved 04/18/2018
-Adding and removing study team members, approved 06/06/2018
-Modifying assessments, updates to consent and protocol, approved 07/06/2018
-Receipt of Certificate of Confidentiality reported, acknowledged 08/06/2018
-Modified consent to reflect receipt of CoC, approved 08/31/2018
-Continuing Review, approved 09/12/2018
-Added assessment, adding study team member, updated consent per adverse event submitted for MRI, approved 10/26/2018
-Adding study team member, approved 11/07/2018
-Updates to protocol and adding study team member, approved 06/07/19

-Continuing review, approved 07/03/19
-Modification: addition of sharing data with the FITBIR system, approved 01/09/20
-Modification to move stimulation sessions to UNM site that includes recruiting non-Veterans who will be seen only at the UNM site. Also included in this modification is the addition of language to the consent and protocol about possible risks associated with RNI's occurring on 07/31/19 and 09/05/19 and submitted to the IRB on 11/19/19 (see next section). Approved 03/09/20.
-Memo sent to UNM IRB stating that enrollment has been halted due to COVID-19, acknowledged 03/26/20
-Continuing Review, Approved 06/03/20
-Modification to study safety related to COVID-19: updated protocol, consent, and addition of symptom checklist, approved 07/20/20
-Adding and removing study team members, approved 08/17/20
-Updated consent and protocol to allow for electronic merchandise cards for participant visits, approved 12/22/20
-Adding study team member, approved 02/08/21
-Continuing Review, approved 06/01/21
-Adding study team members, approved 06/14/21

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:
-On 09/27/18, participant became distressed during MRI while a technician was adjusting equipment. Although the consent covers some of the potential discomforts (i.e., claustrophobia, loud banging noises), it does not specifically note this type of event. "Harm" is indicated above as it appears that the participant experienced emotional distress that was unexpected. This event is clearly related to study procedures and was resolved by discontinuing the scan and discussing the event with the participant. Participant completed initial MRI without incident. PI met with MRI technicians and staff after this event to discuss the importance of communication during the MRI scan for this study. It is possible that future participants will have PTSD since this study recruits primarily from a veteran population. MRI technicians will only enter the MRI scan room if they communicate with a participant first. Reviewed by UNM IRB and consent modified on 10/26/19.

-On 09/04/18 participant reported a headache during the eye movement task. Testing was paused, virtual reality (eye testing) goggles removed, and the participant was allowed to rest. As session was nearly complete, decision made not to complete session. Once testing was discontinued all symptoms (headache) resolved. Reviewed by UNM IRB and consent modified on 10/26/19.

-On 07/31/2019, M87111517 reported headache and vomited during neurosensory assessment. Submitted as RNI on 11/19/19 with intent to modify consent to indicate this as a risk with this assessment. Consent changes approved 03/09/2020.

-On 09/05/2019, M87103937 reported headache during neurosensory assessment, submitted as RNI on 11/19/19 with intent to modify consent to indicate this as a risk with this assessment. Consent changes approved 03/09/2020.

PROTOCOL (2 of 2 total):

Protocol [VA HRPO Assigned Number]: 17-H245

Title: High-Definition Transcranial Direct Current Stimulation for Sensory Deficits in Complex Traumatic Brain Injury

Target required for clinical significance: 120

Target approved for clinical significance: 120

Submitted to and approved by: Institutional Review Board, New Mexico VA Health Care System (NMVAHCS)

-Initial Approval 11/16/2017

STATUS:

(i) Recruitment

-Number of subjects recruited/original planned target: 314/1000
-Number of subjects screened/original planned target: 162400
-Number of patients enrolled/original planned target: 63/120
-Number of patients completed/original planned target: 55/120 (27 HC, 28 TBI)

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

-Adding study team member, 01/09/2018
-Submitted modifications requested by the DoD Scientific Office, approved 02/26/2018
-Consent and protocol updates, approved 05/11/2018
-Consent and protocol updates, approved 07/20/18
-Adding study team member, approved 08/13/2018
-Adding study team member, approved 09/24/2018
-Continuing Review, approved 10/09/2018
-Updated protocol to reflect use of 10 electrodes, updated recruitment flyer to be clear that we are also recruiting Healthy Controls, approved 01/17/19
-Adding study team member, approved 02/21/19
-Adding study team member, approved 03/04/19
-Updated consent, protocol, & flyer, approved 05/09/19
-Consent audit, passed 5/30/19
-Modification to recruit non-veterans was not approved (on 09/20/19). Per VA IRB, VA policies requires that all participant's including non-Veterans be afforded coverage for Research-related injury and the NMVAHCS has not identifiable resources to commit for payment of research-related injury for non-Veterans.
-Continuing Review, approved 10/10/19
-Consent audit passed, 10/06/19
-Modification to remove study team member, Violet Fratzke, approved 01/09/20
-Modification to move stimulation sessions to UNM site and follow-ups to the VA, approved 02/27/20
-Memo sent to VA IRB stating that enrollment has been halted due to COVID-19, acknowledged 03/19/20
-Full study audit passed 06/29/20

-Removing study team member, approved 08/17/20
-Continuing Review approved 09/16/20
-Consent audit passed, 5/26/21
-Continuing review approved 09/02/21

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:

On 09/05/18, a participant reported mild skin sensations experienced during setup of electrodes for the HD-tDCS session. Impedences monitored before all sessions and a new tDCS machine will arrive next week to replace current machine. Reviewed by IRB on 10/09/18 and deemed to not increase potential harm to participants, no changes recommended.

On 11/22/19, a participant reported having PTSD dreams the previous night, which he attributed to the stimulation. IRB determined that the event (was an isolated occurrence of PTSD-related dreams, not associated with subsequent treatment) was not serious, not anticipated, and not related to the research. No further action is required. No further reporting is required.

6. Products

6.1 ***Publications, conference papers, and presentations***

d) Journal publications:

Nothing to report

e) Books or other non-periodical, one-time publications:
Nothing to report

f) Other publications, conference papers, and presentations:

Rustad J, **Quinn DK**, Noordsy DL, Ivkovic A, Ho P. Innovations in consultation-liaison psychiatry care for Veterans with PTSD and TBI. Symposium presented to the Academy of Consultation-Liaison Psychiatry Annual Meeting, online, November 10-12, 2021.

6.2 ***Journal Publications***

Nothing to report

6.3 ***Books or other non-periodical, one-time publications***

Nothing to report

6.4 ***Other publications conference papers and presentations***

Nothing to report

*6.5 **Websites or other Internet sites***

Nothing to report

*6.6 **Technologies or techniques***

The study team developed a customized, portable, gamified method for assessing for convergence insufficiency and delivering vision therapy. This will be described and disseminated to the public in the form of at least two journal manuscripts, planned for submission in early 2022.

*6.7 **Inventions, patent applications, and/or licenses***

Nothing to report

*6.8 **Other products***

Nothing to report

7 Participants & Other Collaborating Organizations

*7.1 **What individuals have worked on the project?***

Name	**Davin Quinn, MD**
Project Role	Principal Investigator
Research Identifier	**0000-0002-1613-8018**
Nearest person month worked	**36**

Contribution to Project	Dr. Quinn is a Neuropsychiatrist at the University of New Mexico. He coordinates with Drs. Harris-Carriman at the NMVAHCS on planning the recruitment, retention, and conducting of Veterans and Warfighters through the study. He runs meetings and conference calls, and assist the other investigators in oversight and training of research assistants and the research coordinator. Dr. Quinn with Dr. Harris-Carriman oversees the creation and management of the regulatory binder, written updates, progress reports, data safety and monitoring reports, and random audits of the research data performed by the USAMRMC Human Research Protection Office, and maintain compliance with the UNM and NMVAHCS IRBs (the IRBs of record for the study). Dr. Quinn is also involved in the preparation of progress reports, manuscript preparation, presentation of the study's findings, and works closely with appropriate study personnel to make sure that all of the study assessments and procedures are completed as planned.

Name	**Stacey Harris-Carriman MD**
Project Role	Co-Investigator
Research Identifier	
Nearest person month worked	**36**
Contribution to Project	Dr. Harris-Carriman is a Physiatrist at the NMVAHCS. On this project she assists with the coordination of the proposed project at the NMVAHCS site helping to develop a recruitment plan for patients at the Polytrauma Veterans and Warfighters. She will oversee the delivery of brain stimulation paired with sensory training and is currently supporting the training of staff. She provides expertise in the evaluation and screening of sensory system impairments and common comorbidities within the OEF/OIF/OND Veteran population. Dr. Harris-Carriman with Dr. Quinn will oversee the creation and management of the regulatory binder, written updates, progress reports, data safety and monitoring reports, and random audits of the research data performed by the USAMRMC Human Research Protection Office, and maintain compliance with the UNM and NMVAHCS IRBs (the IRBs of record for the study).

Name	**Lindsay Worth**
Project Role	Research Coordinator
Research Identifier	

Nearest person month worked	**36**
Contribution to Project	Lindsay Worth is a Clinical Research Manager at the University of New Mexico. For this study, she is responsible for running the protocol at MRN, UNM, CBRR, and NMVAHCS. Works closely with Drs. Quinn, Harris-Carriman, Mayer, Stephen, Alvarez, and Hoffer to complete trainings in conducting neurobehavioral and sensory system assessments including test scoring and the majority of the data entry. She will schedule assessments and the imaging data acquisition sessions with the research MRI and MEG staff. Currently helping to develop a plan (standard operating procedures) for identifying and recruiting the participants, performing pre-scan screening procedures, conduct neurobehavioral assessments, test scoring, and data entry. She coordinates IRB submissions as needed. She has created and maintains the regulatory binders, binders for signed consent forms and coded hard copies of completed test forms and electronic data. She coordinates and participates in meetings and conference calls.

Name	**Kevin Wilson**
Project Role	Research Scientist
Research Identifier	
Nearest person month worked	**12**
Contribution to Project	Kevin Wilson is a Research Technician at the University of New Mexico. For this study, he is working closely with Drs. Quinn and Harris-Carriman to train in and conduct sensory training and brain stimulation with HD-tDCS. He is supervised by Drs. Quinn and Harris-Carriman during the administration of these therapies. He is helping to develop a plan for scheduling sessions and for identifying and recruiting the participants, performing data entry and scoring. He supports the Research Coordinator in developing and maintaining the regulatory binders and binders for signed consent forms and coded hard copies of completed test forms and electronic data. He participates in meetings and conference calls.

Name	**Marcus Sterling**
Project Role	Research Assistant
Research Identifier	
Nearest person month worked	**16**

Contribution to Project	Marcus Sterling is a Research Technician at the University of New Mexico. For this study, he is working closely with Drs. Quinn and Harris-Carriman to train in and conduct sensory training and brain stimulation with HD-tDCS. He is supervised by Drs. Quinn and Harris-Carriman during the administration of these therapies. He is helping to develop a plan for scheduling sessions and for identifying and recruiting the participants, performing data entry and scoring. He supports the Research Coordinator in developing and maintaining the regulatory binders and binders for signed consent forms and coded hard copies of completed test forms and electronic data. He participates in meetings and conference calls.

Name	**Jude Chavez**
Project Role	Research Scientist
Research Identifier	
Nearest person month worked	**12**
Contribution to Project	Kevin Wilson is a Research Technician at the University of New Mexico. For this study, he is working closely with Drs. Quinn and Harris-Carriman to train in and conduct sensory training and brain stimulation with HD-tDCS. He is supervised by Drs. Quinn and Harris-Carriman during the administration of these therapies. He is helping to develop a plan for scheduling sessions and for identifying and recruiting the participants, performing data entry and scoring. He supports the Research Coordinator in developing and maintaining the regulatory binders and binders for signed consent forms and coded hard copies of completed test forms and electronic data. He participates in meetings and conference calls.
Name	**Michael Hoffer, MD**
Project Role	Co-Investigator
Research Identifier	
Nearest person month worked	**36**
Contribution to Project	Dr. Hoffer is an Otolaryngologist, Otologist/Neurotologist at the University of Miami. His expertise is in the assessment, diagnosis, and treatment of vestibular and auditory disturbances following concussion, and is actively involved in developing various countermeasures against post concussive symptoms. He has been assisting in the final development of the study and has been involved in all aspects of the sensory system evaluation and training component, including data quality assurance planning, and the development of the plan for analysis of data. Dr. Hoffer coordinates with Drs.Quinn, Harris-Carriman, Alvarez, Mayer, and Stephen on the discussing the plan for interpretation of

	sensory outcome in relation to the neuroimaging data. He has been involved in training study staff in the evaluation of subjects with sensory symptoms after traumatic brain injury, participating in conference calls and meetings, assessing study progress, and will draft, coauthor, and edit manuscripts.

Name	**Tara Alvarez, PhD.**
Project Role	Paid Consultant
Research Identifier	**36**
Nearest person month worked	
Contribution to Project	Dr. Alvarez is a Biomedical Engineer at New Jersey Institute of Technology (NJIT). Dr. Alvarez has studied the neuronal activity underlying convergence insufficiency after concussion and has been providing expertise on eye-tracking technology platforms and data analytic methods to be used in the sensory system evaluation of participants as well as the sensory training paradigm paired with brain stimulation. Hehas assisted in the final development of the study, participated in meetings and conference calls, and provided training to study personnel to operate the eye-tracking equipment, acquire and analyze data, and provide quality assurance around these methods. Dr. Alvarez will coordinate with Drs. Quinn, Harris-Carriman, Hoffer, Mayer, and Stephen on the interpretation of sensory outcome in relation to the neuroimaging data.

Name	**Chang Yaramothu, PhD**
Project Role	Research Technician (NJIT)
Research Identifier	
Nearest person month worked	**36**
Contribution to Project	Dr. Yaramothu assisted Dr. Alvarez in setting up and training staff to operate the eye-tracking equipment, acquire and analyze data, and provide quality assurance around these methods.

Name	**Andrew Mayer, PhD**
Project Role	Co-Investigator
Research Identifier	

Nearest person month worked	**36**
Contribution to Project	Dr. Mayer is a Neuropsychologist at the Mind Research Institute in Albuquerque, New Mexico. He is a prolific scientist in the field of neuroimaging of mTBI and has provided expertise on the acquisition and analysis of MRI obtained before and after stimulation and training, as well as the neuropsychological assessments. He has assisted in the final development of the study and is involved in all aspects of the neuropsychological evaluation component, including data quality assurance, and analysis of data. He works with Drs. Quinn, Stephen, Hoffer, and Alvarez to develop a plan for interpreting results of MRI in relation to MEG, multisensory performance, and behavioral data, and with Drs. Quinn around developing methods for use of finite element current modeling to predict response. He has participated in conference calls and meetings, assessing study progress, and will draft, co-author, and edit manuscripts.

Name	**Jessica Richardson, PhD**
Project Role	Co-Investigator
Research Identifier	
Nearest person month worked	**36**
Contribution to Project	Dr. Richardson is a Speech and Language Pathologist at the University of New Mexico. Heis extensively published in the areas of neurorehabilitation for aphasia after stroke, individualized high-definition transcranial direct current stimulation (HD-tDCS) optimization for stroke-induced aphasia, and blinding, safety, and fidelity in brain stimulation studies. Hehas assisted in development and design of the HD-tDCS aspect of the protocol, working with Drs. Quinn to train research staff in methods of conducting randomized controlled trials of brain stimulation, ensuring reproducibility of stimulation parameters and advising on individualization of electrode placement. Hehas participated in conference calls and meetings, assessing study progress, and will draft, co-author, and edit manuscripts.

Name	**Julia Stephen, PhD**
Project Role	Co-Investigator
Research Identifier	
Nearest person month worked	**36**

Contribution to Project	Dr. Stephen is a Physicist at the Mind Research Institute in Albuquerque, New Mexico. Hehas studied auditory, visual, and eye-tracking responses with MEG in multiple clinical populations, and has provided expertise on the acquisition and analysis of MEG obtained before and after stimulation and training. Hehas been working with Drs. Quinn, Mayer, Hoffer, and Alvarez to develop a plan for interpreting results of MEG in relation to MRI, sensory performance, and behavioral data. Hehas assisted in the final development of the study and is planning a training for study personnel to perform MEG scanning, acquire and analyze data, and provide quality assurance around these methods. Hehas participated in conference calls and meetings, assessing study progress, and will draft, co-author, and edit manuscripts.
Name	**Marom Bikson, PhD**
Project Role	Unpaid Consultant
Research Identifier	
Nearest person month worked	**0**
Contribution to Project	Dr. Bikson is a Biomedical Engineer who works with the City College of New York and New York Center for Biomedical Engineering. His lab developed HD-tDCS as well as finite element modeling of electric current in brain tissue, and he will provide as-needed input on the design, safety, and parameters of the brain stimulation component of the study, as well as data analytic methods for producing individualized models of current flow to be used as predictors of efficacy. He has been providing consultation about HD-tDCS for this study.

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

Davin Quinn, MD: His support did not change.

Andrew Mayer, PhD: His support from NIH increased between 11/1/20 and 10/31/21.

Support that ended this past year include: Siemens MAGENTOM Prisma/Prismafit Upgrade (PI Mayer), 0.12 calendar months, 2018-2021

Support that started: 18/24 The Healthy Brain and Child Development National Consortium (Bakhireva/Leeman (MPI)), 1.2 calendar months, 2021 - 2026

Tara Alvarez, PhD: Her support did not change.

Julia Stephen, PhD: Her support did not change.

Michael Hoffer, MD: His support did not change.

Chang Yaramothu, PhD: His support from NSF and NIH increased between 11/1/20 and 10/31/21.

Title:	Screening Protocol for Oculomotor Dysfunction
Effort:	1.8-month hours
Supporting Agency:	National Science Foundation
Grants Officer:	Henry Ahn
Performance Period:	06/2021 to 05/2023
Funding Amount:	
Project Goals:	Develop an automated virtual reality vision screening platform
Specific Aims:	Design and prototype a virtual reality platform with eye tracking that can automatically screen for various vision and binocular dysfunction. Perform bench testing for system validation.

Title:	Functional Mechanisms of Neural Controls in Post-Concussive Convergence Insufficiency
Effort:	1.0-month hours
Supporting Agency:	National Institutes of Health
Grants Officer:	Houman Araj
Performance Period:	09/2021 to 08/2026
Funding Amount:	
Project Goals:	Discovery the underlying neural mechanism of office-based vergence and accommodative therapy in adolescents
Specific Aims:	Discover the difference between controls and adolescents with convergence insufficiency concussion

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

Organization Name: New Mexico Veterans Affairs Health Care System

Location of Organization: Albuquerque, NM

Partner's contribution to the project:

a) In-kind support: NMVAHCS has provided research administrative support for the study, including helping study staff obtain Without Compensation Status at NMVAHCS, obtaining access for study staff to medical records, and providing IRB oversight.
b) Facilities: NMVAHCS has provided research space to conduct brain stimulation sessions, including computers for accessing medical records.
c) Collaboration: NMVAHCS has permitted Dr. Harris-Carriman, physiatrist of the Polytrauma Support Clinic, protected time to collaborate with Dr. Quinn in the conduct of this study. They have also permitted access to the Polytrauma population of Veterans with TBI.

Organization Name: Mind Research Network

Location of Organization: Albuquerque, NM

Partner's contribution to the project:

a) Financial support:
b) In-kind support: MRN has provided free matching scans (20 MRI/MEG scans) to assist with study aims. They have made available their technological support staff for data storage (COINS), imaging analysis, training, and FITBIR curation.
c) Facilities: MRN is the site of the MEG and MRI that are currently used in the study protocol.
d) Collaboration: Drs. Mayer and Stephen are content experts and collaborators who provide as-needed expertise for MRI and MEG issues.

Organization Name: New Jersey Institute of Technology

Location of Organization: Newark, NJ

Partner's contribution to the project:

a) Collaboration: Drs. Alvarez and Yaramothu are collaborators who provide content expertise on eye tracking, data analysis and quality assurance, and technical expertise in the setup and training of the oculomotor assessment portions of the study.

Organization Name: University of Miami

Location of Organization: Miami, FL

Partner's contribution to the project:

a) Collaboration: Dr. Michael Hoffer is a collaborator who provides content expertise on neurosensory and TBI assessment, and has assisted with designing and refining the study protocol, as well as analyzing data.

8 Special Reporting Requirements:

Quad Charts: Updated quad chart included.

9 Appendices (attached)

No appendices at this time.