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

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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.

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

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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 -Adding study team members, approved 06/14/21 -Updated flyer for recruiting healthy control participants, approved 10/27/21 -Adding study team members, approved 12/06/21 -Adding study team member, approved 01/19/22 -Continuing review approved 05/18/2022 **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 -Consent audit passed, 05/05/2022 -Continuing Review approved 08/10/22			
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	Annually	100%	Ongoing

-Continuing Review, approved 06/01/21 -Continuing review approved 05/18/2022 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 -Continuing review approved 09/02/21 -Consent audit passed, 05/05/2022 -Continuing Review approved 08/10/22			
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	4-8	100%	04/2018

Development of flow charts, Standard Operating Procedures for all protocol components, COINS data capture system, and data analysis tools complete.			
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 *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.*	8-36	100%	Ongoing
Participants complete testing and intervention over 3 weeks, N = 120 # Potential subjects identified: 356 # Screened by phone: 186 (67 HC, 119 TBI) # Enrolled: 78 (36 HC, 42 TBI) # Completed Visit 1: 76 (35 HC, 41TBI) # Completed stimulation: 32 (32 TBI) # Completed Visit 2: 32 (32 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: 29 (29 TBI) # Completed 6-month call: 28 (28 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	50%	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***	36-48	50%	Ongoing

presented to MOMRP FY21 Auditory, Vision, and Vestibular In Progress Review Meeting, July 20-21, 2021. Preliminary data on MEG and neurosensory symptoms at baseline presented to MHSRS conference, September 12-15, 2022.			
Upload data to FITBIR for data sharing *FITBIR compatibility of data storage complete. Upload will be done as study data is obtained.* ***Common Data Element and Unique Data Element assessment performed with FITBIR. Construction of upload pipeline with collaborators complete.***	36-48	50%	Ongoing

*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: Funding for the study formally ended at the end of this year. A 2nd no-cost extension (NCE) for 6 months was requested by the study team to conduct data analysis following the completion of enrollment and was approved. Subawards were reconciled and closed out for the 1st NCE year. Investigator meetings now focus on data analysis and publication.

(c) Personnel: No new study staff were added during this year.

(d) Scientific: A total of 78 participants (36 Healthy Controls and 42 TBI) were enrolled, as of the end of this year, and the end of funding. A total of 35 of the TBI participants completed the treatment as indicated. The final participants were enrolled and conducted through the protocol in October 2022. The recruitment goals for controls in Specific Aim 2 were essentially met, with 36 control subjects enrolled to serve as a baseline-only comparison group to validate previous findings. Although recruitment goals of TBI participants for Specific Aim 1 and 2 were not met (42 participants instead of 80) due to the pandemic and halt of study activities, we were able to administer the protocol to enough participants that it was the largest study to date using HD-tDCS for postconcussive symptoms in Veterans, and will still provide important data on effect size and correlates of response.

3.2 Specific Objectives

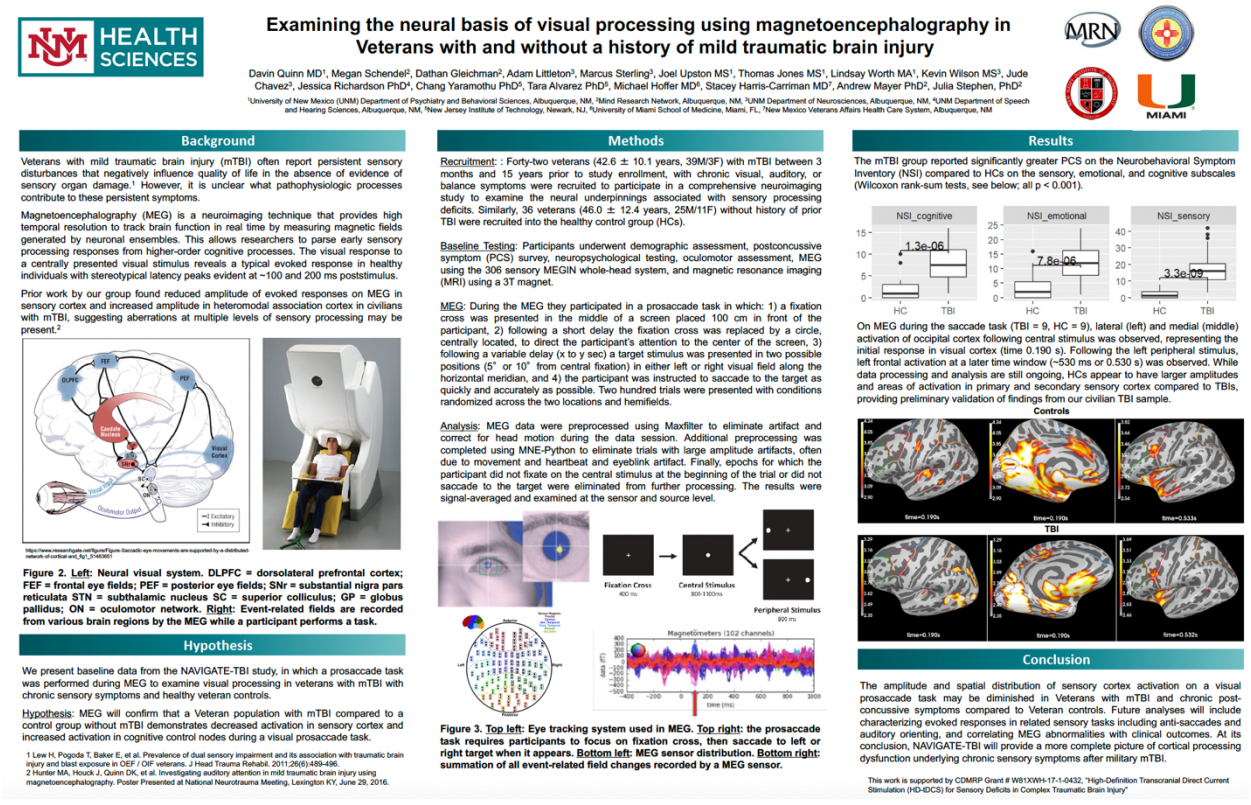
The specific objectives of the study are:

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

In this study period, we concluded enrollment and began analysis of our magnetoencephalography data. Initial results which were presented at the 2022 MHSRS conference (see below) indicate significant differences at baseline between controls and mTBI Veterans with regard to activation of sensory cortex during visual saccade task. In the next study period we will complete processing of magnetoencephalography data and generate final group comparisons between controls and mTBI patients at baseline, and between mTBI patients prior to and after intervention.



Examining the neural basis of visual processing using magnetoencephalography in Veterans with and without a history of mild traumatic brain injury

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Background

Veterans with mild traumatic brain injury (mTBI) often report persistent sensory disturbances that negatively influence quality of life in the absence of evidence of sensory organ damage.[1] However, it is unclear what pathophysiologic processes contribute to these persistent symptoms.

Magnetoencephalography (MEG) is a neuroimaging technique that provides high temporal resolution to track brain function in real time by measuring magnetic fields generated by neuronal ensembles. This allows researchers to parse early sensory processing responses from higher-order cognitive processes. The visual response to a centrally presented visual stimulus reveals a typical evoked response in healthy individuals with stereotypical latency peaks evident at ~100 and 200 ms poststimulus.

Prior work by our group found reduced amplitude of evoked responses on MEG in sensory cortex and increased amplitude in heteromodal association cortex in civilians with mTBI, suggesting aberrations at multiple levels of sensory processing may be present.[2]

Figure 2. Left: Neural visual system. DLPFC = dorsolateral prefrontal cortex; FEF = frontal eye fields; PEF = posterior eye fields; SNr = substantial nigra pars reticulata STN = subthalamic nucleus SC = superior colliculus; GP = globus pallidus; ON = oculomotor network. Right: Event-related fields are recorded from various brain regions by the MEG while a participant performs a task.

Hypothesis

We present baseline data from the NAVIGATE-TBI study, in which a prosaccade task was performed during MEG to examine visual processing in veterans with mTBI with chronic sensory symptoms and healthy veteran controls.

Hypothesis: MEG will confirm that a Veteran population with mTBI compared to a control group without mTBI demonstrates decreased activation in sensory cortex and increased activation in cognitive control nodes during a visual prosaccade task.

1 Lew H, Pogoda T, Baker E, et al. Prevalence of dual sensory impairment and its association with traumatic brain injury and blast exposure in OEF / OIF veterans. J Head Trauma Rehabil. 2011;26(6):489-496.
2 Hunter MA, Houck J, Quinn DK, et al. Investigating auditory attention in mild traumatic brain injury using magnetoencephalography. Poster Presented at National Neurotrauma Meeting, Lexington KY, June 29, 2016.

Methods

Recruitment: : Forty-two veterans (42.6 ± 10.1 years, 39M/3F) with mTBI between 3 months and 15 years prior to study enrollment, with chronic visual, auditory, or balance symptoms were recruited to participate in a comprehensive neuroimaging study to examine the neural underpinnings associated with sensory processing deficits. Similarly, 36 veterans (46.0 ± 12.4 years, 25M/11F) without history of prior TBI were recruited into the healthy control group (HCs).

Baseline Testing: Participants underwent demographic assessment, postconcussive symptom (PCS) survey, neuropsychological testing, oculomotor assessment, MEG using the 306 sensory MEGIN whole-head system, and magnetic resonance imaging (MRI) using a 3T magnet.

MEG: During the MEG they participated in a prosaccade task in which: 1) a fixation cross was presented in the middle of a screen placed 100 cm in front of the participant, 2) following a short delay the fixation cross was replaced by a circle, centrally located, to direct the participant's attention to the center of the screen, 3) following a variable delay (x to y sec) a target stimulus was presented in two possible positions (5˚ or 10˚ from central fixation) in either left or right visual field along the horizontal meridian, and 4) the participant was instructed to saccade to the target as quickly and accurately as possible. Two hundred trials were presented with conditions randomized across the two locations and hemifields.

Analysis: MEG data were preprocessed using Maxfilter to eliminate artifact and correct for head motion during the data session. Additional preprocessing was completed using MNE-Python to eliminate trials with large amplitude artifacts, often due to movement and heartbeat and eyeblink artifact. Finally, epochs for which the participant did not fixate on the central stimulus at the beginning of the trial or did not saccade to the target were eliminated from further processing. The results were signal-averaged and examined at the sensor and source level.

Figure 3. Top left: Eye tracking system used in MEG. Top right: the prosaccade task requires participants to focus on fixation cross, then saccade to left or right target when it appears. Bottom left: MEG sensor distribution. Bottom right: summation of all event-related field changes recorded by a MEG sensor.

Results

The mTBI group reported significantly greater PCS on the Neurobehavioral Symptom Inventory (NSI) compared to HCs on the sensory, emotional, and cognitive subscales (Wilcoxon rank-sum tests, see below; all $p < 0.001$).

On MEG during the saccade task (TBI = 9, HC = 9), lateral (left) and medial (middle) activation of occipital cortex following central stimulus was observed, representing the initial response in visual cortex (time 0.190 s). Following the left peripheral stimulus, left frontal activation at a later time window (~530 ms or 0.530 s) was observed. While data processing and analysis are still ongoing, HCs appear to have larger amplitudes and areas of activation in primary and secondary sensory cortex compared to TBIs, providing preliminary validation of findings from our civilian TBI sample.

Conclusion

The amplitude and spatial distribution of sensory cortex activation on a visual prosaccade task may be diminished in Veterans with mTBI and chronic post-concussive symptoms compared to Veteran controls. Future analyses will include characterizing evoked responses in related sensory tasks including anti-saccades and auditory orienting, and correlating MEG abnormalities with clinical outcomes. At its conclusion, NAVIGATE-TBI will provide a more complete picture of cortical processing dysfunction underlying chronic sensory symptoms after military mTBI.

This work is supported by CDMRP Grant # W81XWH-17-1-0432, "High-Definition Transcranial Direct Current Stimulation (HD-tDCS) for Sensory Deficits in Complex Traumatic Brain Injury"

3.3.1 ***Other Achievements***

Nothing to report.

Stated Goals Not Met

By conclusion of this study period and the formal end of funding, the only study goals not met at the time of this annual report are the stated recruitment goals: 80 TBI subjects and 40 healthy control subjects were anticipated to have been enrolled by end of Year 5, whereas the study has recruited 42 TBI subjects and 36 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.

Despite this, the recruitment goals for healthy controls were nearly met, and the number of participants successfully recruited makes this the largest study to date of HD-tDCS for postconcussive neurosensory symptoms in Veterans.

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?***

As mentioned above, a poster was presented at the MHSRS 2022 conference.

3.6 ***Planning***

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

With approval of the 2nd no-cost extension, the study team will have an additional 6 months to analyse data and generate the final scientific products of the study. We expect there will be at least 2 papers to publish, on the baseline comparison between healthy controls and mTBI patients with regard to magnetoencephalography, and on the effectiveness of HD-tDCS for postconcussive symptoms and associated changes in brain activation.

4. Impact

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

The study team previously 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.
We have also shown that it is possible to generate individualized stimulation montages for patients, and have identified key challenges and principles that must be negotiated when conducting a precision brain stimulation study such as this.

4.2 What was the impact on other disciplines?

Nothing to report at this time.

4.3. What was the impact on technology transfer?

A next-step randomized controlled clinical trial was proposed and funded to validate independently the virtual reality technology developed by Co-I Yaramothu and Alvarez at New Jersey Institute of Technology.

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

Nothing to report at this time.

5. Changes/Problems

5.1 Changes in approach and reasons for change

None at this time. We have concluded data collection, and will now be conducting data analysis for the next study period.

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

a) Personnel effort: team members involved in data analysis have needed to take time off from work due to pandemic-related and personal reasons. They are anticipated to be back at work at the beginning of the calendar year and data analysis will resume.

5.3 Changes that had a significant impact on expenditures

Nothing to report. The 2nd no-cost extension will not be accompanied with funding.

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: 356/1000
-Number of subjects screened/original planned target: 186/400
-Number of patients enrolled/original planned target: 78/120
-Number of patients completed/original planned target: 67/120 (35 HC, 32 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
-Updated flyer for recruiting healthy control participants, approved 10/27/21
-Adding study team members, approved 12/06/21
-Adding study team member, approved 01/19/22
-Continuing review approved 05/18/2022

(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: 356/1000
-Number of subjects screened/original planned target: 186/400
-Number of patients enrolled/original planned target: 78/120
-Number of patients completed/original planned target: 67/120 (35 HC, 32 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
-Consent audit passed, 05/05/2022
-Continuing Review approved 08/10/22

(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

b) Journal publications:

Nothing to report

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

d) Other publications, conference papers, and presentations:

Quinn DK, Gleichman D, Schendel M, Littleton A, Sterling M, Wilson JK, Chavez J, Upston J, Jones TR, Worth L, Richardson JD, Yaramothu C, Alvarez TL Hoffer M, Harris-Carriman S, Mayer AR, Stephen J. Examining the neural basis of visual processing using magnetoencephalography in Veterans with and without a history of mild traumatic brain injury. Poster presentation at the Military Health System Research Symposium, Kissimmee, FL, September 12-15, 2022.

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***

Nothing to report

*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	**48**

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	**48**
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	**48**
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	**24**
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	**28**

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	**24**
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	**48**
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	**48**
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	**48**
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	**48**
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	**48**
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	**48**

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, Chang Yaramothu PhD, Tara Alvarez PhD: Their support from DoD increased:

"Eye Recovery Automation for Post-Injury Dysfunctions (iRAPID)" (PI: Yaramothu). Department of Defense CDMRP FY21 TBIPHRP Clinical Trial Award. Total Costs: 09/01/2022-08/31/2026. Purpose: to conduct a clinical trial of VERVE, a virtual reality platform for delivering automated vision therapy for post-concussion convergence insufficiency in Veterans with mild traumatic brain injury.

Davin Quinn MD, Andrew Mayer PhD: Their support from DoD increased:

"A Prospective Observational Study on Therapeutic and Adverse Effects of Medical Cannabis for Chronic Traumatic Brain Injury." Department of Defense CDMRP FY221 TBIPHRP Clinical Research Award. Total Costs: 10/01/2022-09/30/2025. Purpose: To use advanced

neuroimaging techniques to quantify changes in brain function in Veterans with traumatic brain injury taking medical cannabis.

Julia Stephen, PhD: Her support from NIH increased:

R01 AA029605, Stephen (PI), 9/1/2022-6/30/2027
"Attending to all children: Examining the role of alpha oscillations in attention in young children with and without prenatal alcohol exposure (AsCENd)"

Michael Hoffer, MD: His support did not change.

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 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.