PROTOCOL TITLE:

High-Definition Transcranial Direct Current Stimulation for Sensory Deficits in Complex TBI

PRINCIPAL INVESTIGATOR:

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DATE:

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REGULATORY FRAMEWORK:

Please indicate all that apply:

x	DOD (Department of Defense)
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Is this a clinical trial under ICH-GCP E6? x Yes ☐ No

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1. Objectives

Aim 1: To use magnetoencephalography (MEG) and structural magnetic resonance imaging (MRI) in Veterans and Active Duty Service members, and civilians with mTBI and sensory postconcussive symptoms to demonstrate the mechanism of therapeutic benefit of HD-tDCS for sensory symptoms, as shown by reliable changes in the functional connectivity between the cognitive control network (CCN) and sensory system network (SSN) following stimulation;
Aim 2: this intervention will result in long-term improvements in measures of executive function, depression/anxiety, and quality of life.

These objectives were *formulated* based on a) our extensive clinical experience treating patients with TBI and postconcussive symptoms (PCS); b) our previous studies of network dysfunction in TBI and other disorders using functional MRI and MEG; and c) our pilot data showing improvements in executive function and PCS in TBI patients following tDCS and training.

2. Background

Arguably the most common and disabling postconcussive symptoms (PCS) after a traumatic brain injury (TBI) occur in the sensory systems, and include vestibular (dizziness, nausea), visual (difficulty reading, blurry vision), and auditory (tinnitus, effortful comprehension) disturbances.[1,2] Subject who sustain a mild TBI (mTBI) frequently report symptoms in multiple sensory domains, despite a significant percentage having normal visual and auditory acuity.[3,4] These findings suggest that sensory symptoms arise not from a problem with sensory cortex itself but from a problem with "top-down" processing of sensory information. This processing may be conceptualized as the communication between two distinct brain networks: a unimodal sensory system network (SSN) that receives and refines sensory inputs (i.e. visual or auditory cortices) and a cognitive control network (CCN) of prefrontal and temporo-parietal association areas that integrates, interprets, and prioritizes multisensory data.[5,6] Cognitive control deficits are commonly found in mTBI;[5,9] utilizing functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG), we have documented abnormalities in CCN activation during visual and auditory attention tasks, as well as top-down attention-related modulations (ARMs) of SSNs by the CCN in mTBI patients.[6,8] Eye movement abnormalities are also prevalent after TBI,[2,9] and our group has used eye-tracking technology with both fMRI and MEG to identify nodes in the visuomotor control network that overlap with auditory and visual SSNs.[10,11] Our recent findings confirm earlier work suggesting the combination of MRI with MEG (termed *magnetic source imaging or MSI*) is significantly more sensitive than other modalities such as electroencephalography (EEG) for detecting subtle sensory dysfunction after mTBI.[9,12] This sensitivity is due to the high spatial resolution (~3 millimeter) of MRI, when combined with the high temporal resolution (< 1 millisecond) of MEG, that allows precise measurement of the brain's magnetic fields.

Despite our ability to identify top-down processing deficits underlying sensory PCS, proven treatments that specifically address these deficits are few. N-acetylcysteine and vestibular training are recommended for acute and subacute concussions, but are understudied in intractable cases, and may require frequent office visits over prolonged periods to ensure efficacy.[13] New tools are needed that can "normalize" aberrant CCN activity to rapidly reduce symptom burden (which goes above and beyond the sensory domain?) and improve quality of life. One intervention that holds significant promise is *high-definition transcranial direct current stimulation (HD-tDCS)*. HD-tDCS is a well-tolerated, non-invasive, Non-Significant Risk technique that utilizes focused electrical fields applied through the scalp to modulate neuronal excitability. *To date, HD-tDCS has never been studied for sensory dysfunction after TBI*. Unlike transcranial magnetic stimulation, HD-tDCS has negligible seizure risk and can easily be paired with simultaneous rehabilitation. Over the last four years our group has conducted numerous successful investigations into the mechanisms of tDCS cognition-enhancing effects in both healthy and neurologically impaired populations.[14–16] We are currently running a NIH-funded study of tDCS for chronic PCS after mild-moderate TBI, and initial pilot data from this trial indicate significant reduction in PCS and improvements in executive function with stimulation paired with cognitive training. We have also developed highly detailed, computational finite element models

demonstrating that HD-tDCS can more precisely steer current to specific neural networks by using a greater number of electrodes than traditional sponge-based tDCS.[16,17] Thus we are well-prepared to explore HD-tDCS as an intervention to target aberrant CCN activity identified with MSI.

3. Study Design

We will recruit 120 participants ages 18-69 for the study: 80 participants with mTBI ("intervention participants"), and 40 non-TBI healthy subjects ("healthy controls"). Military TBI population participants will participate in two components to the study—one component at the NMVAHCS, and one component at the UNM Center for Brain Recovery and Repair (UNM CBRR)—each with its own consent and protocol, and governed by its respective Institutional Review Board. Military population healthy controls will only participate at the UNM CBRR. Civilian TBI and healthy control populations will only participate at the UNM CBRR. All study activities occurring at UNM CBRR will be supervised by the UNM HSC IRB.

For the purposes of UNM IRB review, this document will discuss in detail only the aspects of the protocol which take place at UNM/MRN.

Aspects of the protocol which take place at the NMVAHCS (i.e., Some long-term follow-up visits with Veterans may take place at the NMVAHCS if they prefer to complete these visits in-person and some recruitment activities)will be reviewed by the NMVAHCS IRB Committee. Finally, the USAMRMC IRB will review both protocols to ensure compliance with Department of Defense Human Research Protections regulations.

There are a total of 17 visits for this study:

- 2 visits to complete Baseline assessments
- 10 visits to complete Stimulation
- 2 visits to complete Post-Stimulation assessments3 Long-term follow-up visits (either by phone or in-person)
-

Recruitment populations will include the following:
Military TBI and military healthy control populations: Patients from the NMVAHCS Polytrauma Clinic, the Kirtland Air Base 377th Medical Group Clinic, and community dwelling Veterans and Active Duty Service Members.
Civilian TBI and civilian healthy control populations: civilians in the community or referred by clinicians.

Qualifying TBI intervention (both military and civilian) participants will have a mild TBI with chronic sensory PCS (auditory, visual, and/or vestibular) reported on the Neurobehavioral Symptom Inventory (NSI) and normal hearing and visual acuity.

After screening and consent, all participants (military and civilian; TBI and healthy controls) will undergo demographic survey and neuropsychological assessment at the UNM CBRR Clinical Core. Common Data Elements (CDE) instruments, of depression, post-traumatic stress disorder (PTSD), and the quality of life questionnaire will be collected. Participants will then undergo structural MRI scanning and MEG scanning at the Mind Research Network (MRN) at UNM, adjacent to the CBRR. During the 60-minute MEG session, participants will perform tests of auditory orienting, visual attention, and pro/anti-saccades using eye-tracking, while event-related changes in brain activity are recorded. All data will be entered and stored securely in the MRN Collaborative Informatics and Neuroimaging Suite (COINS).

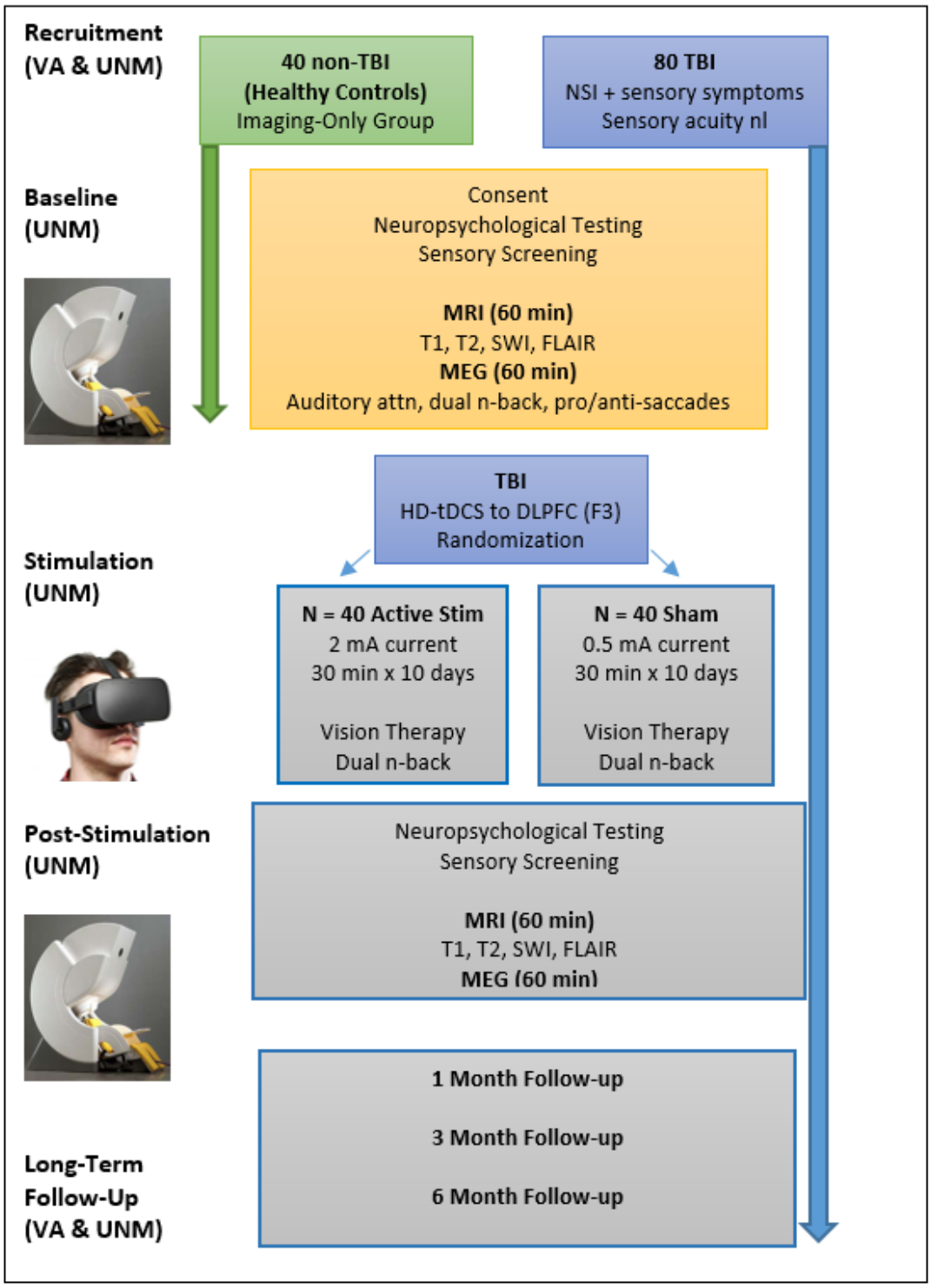
All TBI participants (military and civilian) will receive either active or sham anodal HD-tDCS to the left DLPFC for a total of 30 minutes each day for ten consecutive weekdays at the University of New Mexico Center for Brain Recovery and Repair. After the intervention, TBI participants will then repeat all

demographic, cognitive, and imaging assessments. MEG sources will be reconstructed within individual MRIs to create pre- and post-treatment MSI current distribution models for each task. ***(Aim 1.)***

Followup Visits:
Military TBI participants: At 1, 3, and 6-months post-stimulation, intervention participants will be surveyed regarding symptom burden and quality of life using the NSI, PGIC, and Promis-29. ***(Aim 2.)*** These assessments will be overseen by the NMVAHCS IRB.

Civilian TBI participants. At 1, 3, and 6-months post-stimulation, intervention participants will be surveyed regarding symptom burden and quality of life using the NSI, PGIC, and Promis-29. These assessments will be overseen by the UNM IRB.

The main behavioral outcome variable is degree of improvement in sensory processing tests and symptom severity. MSI outcome variables are the changes in event related field source strength and latency during auditory, visual, and saccades tasks. Secondary outcome variables include changes in accuracy on cognitive control tasks PTSD and depression symptoms, and quality of life ratings.



4. Inclusion and Exclusion Criteria

Inclusion Criteria

Out of the total 120 subjects to be recruited, 80 TBI subjects (Veterans, Active Duty, and civilians) will

be recruited to undergo the full protocol, while an imaging-only control group of 40 non-TBI subjects (Veterans, Active Duty Service Members, and civilians) will be recruited to undergo only the initial baseline assessments. This imaging-only group will have the same inclusion and exclusion criteria except they will not have had a head injury. Subjects will be enrolled in this study if they 1) are aged 18-69, 2) have suffered a mild TBI (alteration in neurological functioning < 24 hours, loss of consciousness (LOC) less than 30 minutes, Glasgow coma scale (GCS) score (if available) of between 13 and 15 acutely, and less than 24 hours of post-traumatic amnesia (PTA); 2) were injured between 3 months and 20 years ago; 3) have post-traumatic sensory symptoms as evidenced by endorsing at least 2 out of 12 sensory symptoms on the Neurobehavioral Symptom Inventory (NSI), a measure of post-traumatic symptoms from the NIH Common Data Elements (CDE) to a severity of "3" or higher, 4) are fluent in English, 5) have been on stable doses of any psychotropic medications for the past 2 months. The imaging-only group will have the same inclusion and exclusion criteria except they will not have had a head injury. All military TBI subjects will have enrolled in the NMVAHCS portion of the study prior to enrollment in the UNM portion.

Exclusion Criteria

Subjects will be excluded from participation in this study if there is 1) any history of moderate or severe TBI; 2) a prior history of other neurological disease or any history of seizures beyond immediate post-traumatic seizure, to as to reduce risk of exacerbation of epilepsy or other neurological symptoms; 3) history of psychosis, so as to reduce risk of psychiatric decompensation; 4) history of current or recent (within two years) substance/alcohol dependence, to reduce confounding effects on cognition and plasticity; 5) any discontinuity in skull electrical conductivity (i.e., unhealed burr holes in scalp) or artificially constructed (metal or plastic) craniotomy cover, to reduce risk of unimpeded electrical current; 6) presence of any implanted electrical device (e.g. pacemaker), to reduce risk of device malfunction; 7) recent medical hospitalization (within three weeks), to reduce risk of medical decompensation during the study; 8) any condition that would prevent the subject from completing the protocol; 9) appointment of a legal representative, as assessed via direct inquiry of the subject and a designated trusted other, to avoid coercion of a vulnerable population; 10) any significant blindness, to screen out peripheral sensory damage; 11) any significant deafness beyond mild hearing loss, to screen out peripheral sensory damage; 12) any ongoing litigation related to TBI, to prevent interference with legal proceedings; 13) any contraindication to MRI; 14) membership in an identified vulnerable population, including minors, pregnant women, and prisoners, so as to prevent coercion.

5. Number of Subjects

120 subjects will be recruited in total: 80 patients with mild TBI will be recruited for the imaging + stimulation arm, while 40 non-TBI healthy controls will be recruited for the imaging-only group. Clark and colleagues found an effect size of Cohen's d = 1.2 for tDCS to induce improvements in cognition.[21] For our power calculations we will assume a more conservative effect size of d = 0.7 which is consistent with a recent meta-analysis of tDCS effect sizes.[18] With 40 tDCS treatment patients compared to 40 sham patients and an effect size of 0.7, we have 80% power to detect effects of active versus sham treatment in a two-sample t-test.

6. Study Timelines

The duration of an individual subject's participation in the research may range up to 6 months. The duration anticipated to enroll all subjects is 4 years. The expected duration for the investigators to complete the study (complete analysis) is 6 years.

7. Study Endpoints

Primary endpoints: change in score on the somatic subscale of the Neurobehavioral Symptom Inventory, Beck Depression Inventory-II, change in MEG activations, and Patient's Global Impression of Change (PGIC) quality of life measure from time 0 to 6 months.

8. Research Setting

All testing, analytical, and research activities will take place at the Clinical Core, UNM Center for Brain Injury Recovery and Repair, and the Mind Research Network, both located in Domenici Hall.

The Clinical Core of the UNM CBRR is a state-of-the-art cognitive neuroscience research facility, specializing in neuropsychological testing, neurophysiological measurement, and noninvasive brain stimulation. It is led by two cognitive neuropsychologists and features a dedicated staff of psychometricians and research technicians to carry out all aspects of Core projects. This includes developing, implementing, and coordinating research and administrative procedures for the successful management of clinical studies; scheduling neuropsychological assessments, neuroimaging appointments, and treatment appointments; and ensuring regulatory compliance of study modifications, events, and audits.

Mind Research Network: MRN is a world-class research organization located in Albuquerque, New Mexico with state-of-the-art imaging and information technologies and services. MRN is headquartered in Pete and Nancy Domenici Hall on the north (medical school) campus of the University of New Mexico (UNM) and occupies 33,000 square feet of space. MRN staff includes approximately 100 employees, 20 graduate students, and 40 volunteers. Domenici Hall is also home to two state-of-the-art animal research facilities: UNM's Biomedical Research and Integrative Neuroimaging (BRaIN) Center, a neuroimaging facility for basic studies of central nervous system pathophysiology in animal models; and UNM's Neurobiology Research Facility (NRF). In addition, Domenici Hall provides all of the human research space for UNM's Departments of Neurology and Psychiatry – both part of UNM's Health Science Center (UNMHSC). Resource sharing and collaboration between UNM and MRN are encouraged by this proximity, as well as by joint academic appointments. Together, UNM and MRN form a unique neuroimaging center for advancing neuroscience research.

9. Resources Available

Principal Investigator

As a junior PI in the UNM Center for Brain Recovery and Repair, Dr. Quinn's goal is to establish an independent NIH-funded research program in neurorehabilitative and neurostimulatory therapies for affective, behavioral, and cognitive sequelae of traumatic brain injury (TBI). The current proposal represents an exciting opportunity for him to bring together several of his academic interests in one scientific endeavor. Dr. Quinn has made the treatment of TBI the focus of his clinical work for the past several years, achieving board-certification in neuropsychiatry and behavioral neurology in 2012 and brain injury medicine in 2016, and establishing a neuropsychiatry clinic in the UNM Clinical Neurosciences Center in 2013 to better serve the undertreated population of TBI patients in New Mexico. Serving as the consultant psychiatrist for the University of New Mexico Hospital since 2009, Dr. Quinn evaluates patients admitted to the hospital to the neurological and neurosurgical services. As UNMH is the only Level 1 trauma center in the state, the vast majority of TBIs receive care at this institution, and Dr. Quinn treats many patients with post-traumatic amotivational, dysexecutive, disinhibition, and psychomotor syndromes resulting from damage to cortical-subcortical circuits. He has followed these patients after their hospitalizations as well, and published several case reports highlighting theoretical and practical dilemmas in treating TBI.

Dr. Quinn joined the UNM Electroconvulsive Therapy (ECT) Service in 2012 after becoming certified in ECT, and in 2013 became the consultant psychiatrist for the UNM Movement Disorders Clinic and their associated deep brain stimulation (DBS) team. He established the UNM Transcranial Magnetic Stimulation Clinic in 2017. He has co-authored a review of longitudinal neuroimaging studies of ECT,

a review of psychiatric symptoms after DBS, and reported the first successful use of right unilateral ECT for catatonia in a patient with a deep brain stimulator.

To assist him in carrying out the proposed research Dr. Quinn has assembled an experienced team of advisors. Dr. Stacey Harris-Carriman, is a board-certified physiatrist and attending physician in the NMVAHCS Polytrauma Clinic, who performs daily evaluations of TBI patients. Dr. Marom Bikson is an expert in high-definition transcranial direct current stimulation, and its mechanisms of action, and will provide key guidance regarding the application of this neurostimulatory technology. Dr. Michael Hoffer is a prolific researcher in the neurosensory symptoms of TBI, and will provide methodological and research design expertise. Additional guidance will be provided by Dr. Andrew Mayer, who is expert in neuroimaging of TBI and methodological issues; Dr. Julia Stephen, who is the MRN MEG Core Director; Dr. Jessica Richardson, who has studied the use of individualized HD-tDCS electrode placement in stroke patients; and Dr. Tara Alvarez, who has designed and optimized virtual-reality-based treatments for post-traumatic oculomotor dysfunction.

Research Coordinator, TBN, 12.0 calendar months/1.0 FTE (Years 1-4)
The Research Coordinator will be responsible for running of the protocol at MRN, UNM CBRR, and NMVAHCS. The research coordinator will work closely with Drs. Quinn, Harris-Carriman, Mayer, Stephen, Alvarez, Richardson, and Hoffer to conduct neurobehavioral and sensory system assessments including test scoring and the majority of the data entry. She/he will schedule assessments, and she/he will also schedule the imaging data acquisition sessions with the research MRI and MEG staff. She/he will be responsible for identifying and recruiting the participants, perform pre-scan screening procedures, conduct neurobehavioral assessments, test scoring, and data entry. This individual will assist the research assistant in maintaining the regulatory binders, screening database, adverse event logs, and minutes of meetings. She/he will also participate in meetings and conference calls. In performing these administrative and regulatory tasks, the RA will work under the supervision of Drs. Quinn and Harris-Carriman.

Research Assistant, UNM, TBN, 6.0 calendar months/0.50 FTE (Years 1-4)
The UNM Research Assistant will be responsible for running of the protocol at NMVAHCS. The research assistant will work closely with Drs. Quinn, and Harris-Carriman to conduct sensory system training and brain stimulation with HD-tDCS. She/he will be supervised by Drs. Quinn and Harris-Carriman during the administration of these therapies. She/he will schedule sessions, and will be responsible for identifying and recruiting the participants, performing data entry and scoring. This individual will assist the study coordinator in maintaining the regulatory binders, signed consent forms, and securing coded hard copies of completed test forms and electronic data. She/he will also participate in meetings and conference calls. In performing these administrative and regulatory tasks, the RA will work under the supervision of Drs. Quinn and Harris-Carriman.

Data Analyst, TBN, 12.0 calendar months/1.0 FTE (Years 1-4)
The Data Analyst will be responsible for data acquisition, storage, curation, statistical analysis, fidelity, and quality assurance at UNM, MRN, and NMVAHCS. The data analyst will work closely with Dr. Quinn and Dr. Harris-Carriman to analyze the MRI, MEG, behavioral, and demographic data, create automated analytical pipelines, troubleshoot performance issues in the data acquisition components of the protocol, conduct statistical analyses, and create data representations for conveyance in meetings, reports, and publications. The data analyst will draft, co-author, and edit manuscripts for publication, and participate in meetings and conference calls.

Neuropsychological Assessment Measures. The Core has a library of advanced neuropsychological tools, applicable to assessment of different aspects of recovery and repair following TBI. The library is useful for subjects of different ages and severity of injury. This library has novel, computer-based neuropsychological measures as well as traditional neuropsychological measures long utilized in neuropsychological research projects and recommended for specific clinical populations (e.g., TBI

NINDS Common Data Elements). The Core maintains an instrument bank of health-outcome measures, including state-of-the-art, computer-administered measures.

2) *NIH Toolbox: Assessment of Neurological and Behavioral Function.* The NIH Toolbox is a state-of-the-art set of standardized instruments developed by NIH to enhance data collection and advance and accelerate the pace of discovery in neuroscience research. The NIH Toolbox is a recently developed set of brief, computerized measures of key neuropsychological functions appropriate for use throughout the lifespan (i.e., 3+ years old) and across diverse study designs and settings.
***Virtual Reality Eye-Tracking Devices*:** An Oculus Rift virtual reality head-mounted display outfitted with ISCAN eye-tracking sensors will be used to characterize oculomotor performance deficits (UNM) during assessments.

3) *Transcranial Direct Current Stimulation (tDCS).* A sponge-based tDCS system (NeuroConn: DC-Stimulator MR) and a high-definition tDCS system (Soterix: MxN tES) are available in the Core for investigators to use to modulate neuronal excitability. These are CE-certified medical devices for conducting non-invasive transcranial direct current stimulation (tDCS), alternating (tACS) or random noise (tRNS) current stimulation on subjects, capable of delivering stimulation through diverse montages for sophisticated current steering. Both devices are equipped to deliver current through a variety of electrode shapes and sizes, with options for double-blind administration, and use in magnetic resonance imaging scanners.

Data and sample collection. The Core will provide expert neuropsychological and electrophysiological assessment technical support. This will include providing testing rooms, neuropsychological tests and supplies, laptop computers, electroencephalography, and neuropsychology technicians/ psychometricians, as well as data entry and storage. Core staff will assist the investigators with scheduling of assessments, neuroimaging, and treatment appointments. The Core will provide space for interventions being studied as part of this research project. Neuropsychological assessment batteries will be administered by Core psychometricians under the supervision of the Core co-directors. Neuropsychological test data will be scored by the psychometricians, with scoring reviewed for accuracy by the supervisors. A neuropsychological test summary prepared by technicians and reviewed by the supervisors will be provided to investigators, participants, and referral sources if indicated. If requested, Core co-directors will also provide feedback to participants regarding neuropsychological assessment results. Participant hardcopy data will be stored in locked file cabinets in locked rooms within a locked, security-patrolled building. For analysis, participant data will be entered and stored in COINS, a web-based electronic data capture platform that is secure and HIPAA compliant available on the MRN server. Neuropsychological data will be entered by psychometrists into study databases with accuracy verified by double entry.

3T MRI and the Elekta Neuromag MEG are housed immediately proximal to the neuropsychological testing rooms, as part of the MIND Research Network (MRN) advanced biomedicalimaging core. The imaging facilities have private changing rooms with lockers for personal items.

Should patients require any medical or psychological care as a consequence of participation in research, UNM Health Sciences Center is located immediately proximal to the CBRR and Mind Research Network and can provide basic to advanced care 24 hours a day, 7 days a week.

10. Prior Approvals

Departmental Approval form included.

11. Multi-Site Research

Plans for communication between the collaborating institutions: Dr. Quinn and Dr. Harris-Carriman will be the head of an Administration and Oversight committee that will consist of study staff and collaborators. They will communicate regularly by e-mail, weekly by conference call with the study coordinator, and in-person at an annual study meeting. The Administration and Oversight component will monitor progress in all aspects of the project and discuss issues concerning recruitment/enrollment, data collection/analysis/entry, preparation of papers and technical problems. This group will also be responsible for oversight of the project, including compliance with ethical guidelines for conduct of human research as regulated by HIPAA and institutional review boards (IRBs), conferring regularly with their project staff to ensure that recruitment and data collection are carried out according to the standardized project protocols and that data are transferred to the research coordinator in a timely manner for entry into the study database. This committee will also be responsible for ensuring that all sites have the most current version of the protocol, consent document, and HIPAA authorization; that all required approvals have been obtained at each site, that all modifications have been communicated to sites, and approved by each site's IRB of record. Any noncompliance with the study protocol will be reported by the PI to the study IRBs of record, as well as the USAMRMC IRB.

Data Safeguarding: Dr. Quinn will manage neuropsychological, demographic, and sensory data entry at UNM. Oversight for imaging data collection and analysis at MRN will be performed by Dr. Stephen and Dr. Mayer. Overall data quality assurance will be conducted by Drs. Quinn and Harris-Carriman. In addition, Dr. Quinn will analyze imaging, cognitive, behavioral, and sensory data, and brain stimulation data from the two sites at least once a month to guarantee that procedures remain consistent throughout the grant period. Drs. Quinn and Harris-Carriman will monitor subject enrollment and address issues that arise. They will communicate by email and telephone weekly and as needed, at which time enrollment will be reviewed so that inclusion/exclusion criterion are observed consistently over all recruitment sites. The secure, password-protected, firewall-protected MRN server will be used to store data from the study sites, including the demographic, neuropsychological, and neuroimaging information collected by individual MRN/University of New Mexico (UNM) investigators during the course of IRB-approved human research. All research data collected in this server is coded with random subject identifiers. If a participant grants permission, this information may be used for unspecified future research. The database is stored on a secure network at MRN and access is password protected.

Standardization of Study Procedures Across Sites: All consenting, cognitive, sensory, behavioral, and clinical measures will be standardized across study staff at CBRR. MRI and MEG scanning will take place at the adjacent MRN, physically located within the same building as CBRR.

Our assessments will follow NINDs recommended Common Data Elements (CDE) and the data protocol currently proposed. In regards to neuroimaging, the same MRI and MEG scanners will be utilized throughout the study, with protocoled procedures for obtaining necessary sequences. At initial grant funding, Dr. Quinn and Dr. Harris-Carriman, in consultation with Drs. Mayer, Stephen, Alvarez, Hoffer, and Richardson, will write standardized project protocols for recruitment (inclusion/exclusion criterion), consenting, screening, administration of brain stimulation and training, administration of cognitive, behavioral, and clinical measures, MRI and MEG safety screening, MRI and MEG data acquisition, neuroimaging data processing and analyses, and data entry. The research coordinator, postdoctoral fellow, and research assistants will be jointly trained in
these standardized project protocols by study investigators.

Real-time communication will be assured by having all investigators and research staff carry cellular phones, with access to all contact phone numbers. They will all agree to be available to answer phone calls from other team members, and if a call is missed, agree to call back within a three-hour time-window.

Plans for data transfer between the collaborating institutions: Appropriate Data Transfer Agreements

will be established according to institutional guidelines of UNM/MRN, and NMVAHCS, and approved by each local IRB. Consent forms for this UNM study will clearly document a participant's permission to store and share any data obtained during the course of the study. Only IRB-approved study personnel will have access to any data collected during the course of this study.

12. Study Procedures

Experimental Design and Methods

Participants: 120 subjects will be recruited for this study, 40 healthy controls subjects for the imaging-only group, and 80 mTBI subjects for the stimulation arm who have suffered mild TBI at least 3 months prior to study enrollment, but not more than 20 years prior to enrollment. All participants will be 18-69 years of age. We will expect to screen approximately 200 patients with mTBI in order to reach our goal of 80 TBI subjects. Recruitment of civilians will be overseen by UNM and recruitment of military subjects will be overseen by the NMVAHCS IRB.

Recruitment: Recruitment of civilians will occur via flyers, clinician referrals, and word of mouth. Military participants (ages 18-69) enrolled in the study protocol at the NMVAHCS will automatically be invited to come to the UNM CBRR to ask questions prior to providing consent (for UNM part of protocol). Healthy control participants will be invited to UNM CBRR to ask questions and complete consent if interested in participating. They will be provided with consent forms that describe the study procedures and potential risks in great detail. If participants are unsure about participation, they will be given our contact information and be invited to call if they decide to participate.Once UNM CBRR informed consent is obtained and the appropriate forms signed, the participant will be assigned a unique research subject identifier (URSI) number, and from that point forward all research data will only be labeled with the URSI number. The key linking identifiers of participants to the URSI will be maintained on a separate database that will be stored behind locked doors, in a locked filing cabinet in a secure area of the CBRR, and on the UNMHSC secure server.

If public health conditions require in-person research encounters be minimized some of the above outlined recruitment procedures may be conducted over the phone. The following outlines phone recruitment procedures:

Military and healthy control participants (ages 18-69) enrolled in the study protocol at the NMVAHCS will automatically be called so that they can ask questions prior to providing consent (for UNM part of protocol). After discussing the study and asking questions, potential participants who complete screening and are eligible for participation, will be mailed or emailed the consent form that describes the study procedures and potential risks in great detail. Participants will be given our contact information and be invited to call if they decide to participate. If they decide to participate, a consent phone call will be conducted in which the consent form is reviewed, the participant can ask questions, and if interested in continuing participation, the Consent Form Quiz will be completed (over the phone). If they are successful with the quiz, they will be scheduled for their first visit. Consent form signature will be done in person, at their first visit, so that it can be witnessed and signed by research staff. Once informed consent is obtained and the appropriate forms signed, the participant will be assigned a unique research subject identifier (URSI) number, and from that point forward all research data will only be labeled with the URSI number. The key linking identifiers of participants to the URSI

will be maintained on a separate database that will be stored behind locked doors, in a locked filing cabinet in a secure area of the CBRR, and on the UNMHSC secure server.All participants (both TBI and healthy control; military and civilian) may then undergo baseline demographic data collection, neuropsychological assessments sensory evaluation, at UNM CBRR. They may also undergo MEG and MRI at the Mind Research Network, located in the same building as CBRR.

The TBI intervention group (military and civilian) will then undergo HD-tDCS and sensory training sessions, which will be delivered over 10 days at UNM CBRR. They will then repeat all testing and assessments that were performed during the baseline visits.

Long-term follow-up will then be performed at 1, 3, and 6 months for the intervention group. For military TBI participants, this will be overseen by the VA IRB. For civilian TBI participants, this will be overseen by UNM.

All assessment items with an asterisk may be over the phone or sent to the participant to complete if public health conditions require in-person research encounters be minimized. Consent will be obtained prior to any study activities.

Demographic Data: As part of the initial assessment, basic demographic data regarding the subject may be noted down, including age, gender, socioeconomic status, educational attainment, medical and mental history, handedness, use of common stimulants such as caffeine, and brain injury severity. They may also be asked if they are willing to allow their medical record to be accessed, for the purposes of confirming details about any TBI as well as obtaining results of neuroimaging studies done at the time of injury or afterward. This will include medical, surgical, neurological and psychiatric history, results of lab tests, brain scans, electroencephalography tests, medication lists, information from doctor's visits and hospital visits.

TBI Diagnosis: will be assessed using:

*Combat Exposure Scale
*Glasgow Outcome Scale
*Ohio State University Identification Method
*Walter Reed Army Medical Center Blast Injury Form

Behavioral Symptoms: will be assessed using:

*Defense and Veterans Pain Rating Scale and Supplement
*Neurobehavioral Symptom Inventory
*PTSD Checklist – Military Version

Quality of Life will be assessed using:

*Patient's Global Impression of Change
*Community Integration Questionnaire
*Promis 29

Neuropsychological testing procedures: All neuropsychological testing will be administered in the Center for Brain Recovery and Repair Core by trained study personnel under direct supervision of core directors, clinical neuropsychologists Drs. Yeo, Campbell, or the PI. The primary dependent outcome variable to be studied is the somatic subscale score on the NSI. The following domains and tests will be administered:

Digit Span Hopkins Verbal Learning Test (HVLT));

Test of Memory Malingering (TOMM);

Test of Premorbid Functioning
Trail Making A and B
NIH Toolbox Assessments
Handedness;

Sensory Assessment: Hearing, balance, and vision will be assessed using CDE instruments:

Vision:

Convergence Insufficiency Symptom Survey (CISS)

Oculomotor Assessment Tool

Visual Acuity (Snellen Chart)
Oculomotor control will be assessed using virtual reality goggles (Oculus DK) with implanted eye trackers (iScan).

Hearing:

Hearing Handicap Inventory

Audiometry

SCAN-3 A
Tinnitus Handicap Inventory

Balance
*Dizziness Handicap Inventory
Neurosensory Assessment

Magnetoencephalography: Magnetoencephalography (MEG) may be done after neuropsychological testing. The participant will sit in the MEG scanner to record brain magnetic fields. MEG setup takes between 10 and 30 minutes, and subsequent recording takes one to two hours. During MEG assessments participants will complete numerous active tasks. Each task is designed to parse different cognitive mechanisms that contribute to sensory performance. In perceptual tasks, participants will discriminate tone pitches amongst novel distracting tones. For eye movement tasks, participants are asked look either towards or away from a visual stimulus.

Magnetic resonance imaging: Structural MRI scan(s) will be obtained for integration with MEG, as needed for MSI analyses. Total scan time, including participant setup and removal, is expected to take 30 minutes to 1 hour. Participants may lie down on a table and be placed into a long donut-shaped magnet. During the scan, participants will be asked to rest quietly or to fixate on a dot on a screen in front of them. In visual decision making tasks, participants are required to classify stimuli based on pre-determined types of rules. No contrast will be used. Any female over 18 will complete a urine pregnancy screen before the MRI scan. Results of pregnancy screens will be kept strictly confidential as per MRN policy. Urine samples will be disposed of immediately after testing.

Left DLPFC anodal HD-tDCS Intervention (Visits #3-12): All TBI participants (military and civilian) will receive either active or sham anodal HD-tDCS to the left DLPFC for a total of 30 minutes each day for ten consecutive weekdays at the University of New Mexico Center for Brain Injury Recovery and Repair. Current will be ramped up over 1 minute at initiation and ramped down over 1 minute with termination. The choice of anodal stimulation was based on our preliminary data and reviewed literature. A longer period of stimulation (2 weeks instead of 1 week) was selected based on evidence that repeated stimulations in close succession result in longer-lasting effects in healthy controls, stroke, and depression, with observed effect up to three months afterward. A Soterix 9-channel high-definition transcranial electrical stimulator system will be used to administer HD-tDCS current. Targeting of the left DLPFC (F3 position, International 10-20 system of EEG coordinates) will be done by utilizing a standard EEG cap fitted snugly to the subject's head. Round, 1 cm^2 HD-tDCS

electrodes will be utilized to deliver anodal current and receive cathodal current. Two anodal electrodes will be placed on the scalp over the DLPFC, delivering approximately 1 mA of current each, to reduce overall sensation. Up to 6 cathodal return electrodes will be placed in cardinal positions around the anode. Current for the treatment condition will be applied at 2.0 mA for 30 minutes for a total delivered charge of 60 mA-min. UNM Co-investigator Dr. Davin Quinn will train the research technician and/or the research coordinator to administer the HD-tDCS.

Double blind design and sham treatment: The sham stimulation (control) group will receive 0.5 mA current for 30 minutes each session with a 1 minute ramp at the beginning and end of treatment. The 0.5 mA current is used as a control condition, rather than the absence of stimulation, to equate aspects of the procedure (preparation and application of electrodes), and to give the participant a degree of physical sensation that is somewhat like that of the 2.0 mA stimulation group while remaining well below the level sufficient to affect brain function and behavior. To accomplish a double blind, the HD-tDCS machine is programmed to randomize sham versus active stimulation and keeps track of the stimulation protocol for later querying.

Sensory Training Tasks (Visits #3-12): For all groups, participants will be administered the sensory training battery for 30-45 minutes, during treatment and sham. While there are multiple sensory modalities that could have been targeted with training, the auditory, visual, and vestibulo-oculomotor systems are the most implicated in PCS. Session procedures will begin with HD-tDCS electrode placement while seated in a comfortable chair. After initiation of HD-tDCS, the first half of the training is a set of vision therapy exercises for convergence insufficiency symptoms after traumatic brain injury, devised and validated by Consultant Alvarez and her colleagues. It is delivered via computer with an Oculus Rift virtual reality headset outfitted with eye-tracking sensors. The exercises consist of 1) disparity vergence steps, where two visual images are presented and the subject attempts to fuse the images by converging with their eyes; 2) disparity vergence ramps, using images moving smoothly inward or outward the subject must focus on; and 3) saccadic stimuli, where subjects are asked to look at visual stimuli in the periphery. These tasks activate a consistent brain network involving nodes of the CCN (DLPFC), frontal eye fields, parietal, cerebellar, and midbrain nodes that is implicated in convergence insufficiency. Thus this task is well suited to pairing with HD-tDCS to activate CCN circuits associated with the vestibulo-oculomotor system.

During the second half of the experiment, subjects will perform our dual visual/auditory n-back task that specifically loads onto CCN circuits in the DLPFC mediating working memory, and has been utilized in our current tDCS trial (Quinn et al, in preparation). In the dual n-back, subjects are asked to look at a sequence of squares displayed on a computer screen, one at a time, in different areas. They must press a button if the current square matches the location of the square from 1, 2, or 3 instances previous. At the same time, a computer-generated voice is stating a string of numbers, one at a time. The subject must also respond with a button press if the current number matches the number from 1, 2, or 3 instances previous. Cognitive load increases as subjects are asked to go from 1, to 2, to 3-back in the task, trying to hold both locations of squares as well as stated numbers in working memory.

Post stimulation testing: the next available weekday following completion of the intervention, subjects will return to UNM CBRR to repeat the demographic, neuropsychological, sensory, and imaging assessments. Participants and research staff will also complete an exit questionnaire after the completion of all assessments and testing.

COVID-19 Assessments

Depending on public health guidelines, participants may complete the following assessments:

Prior to any study visit and upon arrival for visit, participants may complete via text or phone call, the **Participant COVID-19 Symptom Checklist** to assess for any symptoms of COVID-19. If any symptoms are endorsed, the PI will be notified, and the study visit may be cancelled.

The **C**o**R**onav**I**ru**S** Health **I**mpact **S**urvey (CRISIS) V0.3: Adult Self-Report Baseline Current Form **may** be used to assess participant's anxiety related to COVID-19. The demographic questions on this form will not be administered.

Long term followup: At 1 month, 3 months and 6 months after stimulation, military TBI subjects will complete the PCL-M, the NSI, Promis-29, and PGIC quality of life assessment tools at the NMVAHCS or via telephone. This will be overseen by the NMVAHCS IRB. Civilian TBI subjects who are enrolled in the study will complete these follow-ups at UNM CBRR or via telephone. This will be overseen by the UNM IRB.

13. Data Analysis

All data will undergo standard preprocessing (e.g. motion correction, spatial normalization) and quality control prior to statistical modeling. Depending on the specific question of the study, data may be analyzed using the general linear model, independent components analysis, machine learning techniques, or a variety of other standard approaches for neuroimaging data. Drs. Mayer, Stephen, and Alvarez are skilled in analysis of the various behavioral data, sensory performance, MEG and MRI sequences and will assist the PI in analysis of the data.

14. Provisions to Monitor the Data to Ensure the Safety of Subjects

Data safety and monitoring will be carried out to ensure and maintain the scientific integrity of this project and to protect the safety of our participants. Safety monitoring is the process during the study that involves review of accumulated outcome data for groups of subjects to determine if any of the procedures practiced should be altered or stopped. Ultimately, the PI (Quinn) will be responsible for monitoring the safety of the study and complying with the reporting requirements. An independent study monitor, Dr. Christopher Abbott and Sarah Pirio Richardson (Appendix A) , will review the study data on a quarterly basis with the co-PIs to ensure participant safety. Dr. Abbott is a board-certified psychiatrist and NIH-funded clinical investigator in the use of neuroimaging to evaluate mechanisms of action of electroconvulsive therapy, and is thus a highly qualified person to serve as the independent study monitor. Continuous, close monitoring of participant safety will include prompt and frequent reporting of safety data (i.e., adverse/serious adverse events) to the monitor, the University of New Mexico Health Sciences Center Institutional Review Board (UNMHSC IRB) and the USAMRMC staff with oversight responsibility. The PI will provide a summary of the safe conduct of the study to USAMRMC on an annual basis as part of the progress report. All AEs occurring during the course of the study will be collected, documented, and reported to the UNMHSC IRB.

The review of data may result in early termination of the study, amendment to the protocol, or changes to the data collection plan or study forms if it appears that there are adverse events occurring at a rate significantly greater than that found in similar tDCS studies involving subjects with neurological disorders (ie. stroke). Should the protocol or data collection plans or study forms be amended as a result of data review, the IRB will be notified and the amendment approved prior to study amendment implementation. Any substantive changes to the protocol, such as a change in PI, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc), significant change in study design (i.e. would prompt additional scientific review) or a change that could potentially increase risks to subjects, will also be submitted to the USAMRMC IRB. In addition, the participants will be notified of any significant new findings that develop during the course of research that may affect their wish to continue participation in the study.

15. Withdrawal of Subjects

If at any time a participant wishes to withdraw from the study, they will be debriefed by the study coordinator or principal investigator as to the reason for their withdrawal. They will be offered the chance to partially withdraw from the stimulation protocol and continue in the data collection aspect if they so wish. Otherwise the participant will then be thanked for their time, and they will be compensated for the extent of their participation.

If the participant wishes to withdraw, they will be asked if they will allow data already collected on them to be used in the study analysis. If not, the data associated to their identifying code will be purged from the study database.

16. Data Management/Confidentiality

Questionnaire Data: All data are coded with a unique research subject identifier (URSI) number. Electronic data is stored on a drive only accessible by the research team on a secure MRN server, and/or in the COINS database on a secure HIPAA compliant cloud based server. For non-computer based forms, such as the neuropsychological assessments, the data collection sheets are stored in a locked cabinet in a locked office at MRN.

Behavioral and Imaging Data: All data are coded with a unique research subject identifier (URSI) number. Electronic data is collected and stored on a drive only accessible by the research team on a secure MRN server, and/or in the COINS database on a secure HIPAA compliant cloud based server.

Neuropsychological testing, sensory testing, and questions regarding demographics, medical and TBI history, postconcussive symptoms, and quality of life, and neuroimaging will be recorded on to paper and pencil or computerized data forms that do not contain identifying information, and will only be marked with the subject's URSI. A separate file contains contact information for the purpose of providing the radiology review letter and future contact, if needed, but has no personal data or protected health information that is collected as part of the study.

No personally identifying information will be coded on the questionnaires, neuropsychological measures, brain imaging data, or any other data recording instruments, assuring confidentiality to the best of our ability. Subject identification numbers are assigned to each participant. Only the PI and HIPAA-trained project coordinator have access to the file that links names with subject numbers. All data are stored in locked file cabinets in a locked office, and on password-protected computers located behind a secure and maintained firewall.

All data are collected by the PI, or trained research assistants who have completed on-line training in human subjects' research, HIPAA and research integrity; who are trained in our lab on research data management and confidentiality; and who are trained to criterion on project protocol. Data will be collected specifically for this proposed research project.

Participants will be assured that all records will be kept confidential in research files located in a locked office and entered into a password-protected computer located behind a secure and maintained firewall. Breach of confidentiality is highly unlikely because all personally identifying information will be kept separate from data collected, and will be linked only by a master subject identification list maintained by the project coordinator and PI.

In order to address any concerns regarding coercion, participants will be informed that they are free to choose not to participate and may withdraw at any time (this is included in the consent form).

Finally, because any information gathered as part of this study is confidential, we cannot intervene on an individual level unless it is discovered that there is imminent threat to the life of the participant, to others, or if there is any indication of child or elder abuse. In these rare cases, we would consider the risk to self and others and intervene as we would if the individual endorsed other intent to harm

themselves (i.e., talk with the participant and express concern, present the participant with local options for treatment, encourage him/her to disclose the issue to authorities, and if unwilling, inform them that we must disclose the information to authorities for their (or others') safety.

We will also provide all participants and their families with a referral list of community support, treatment, and educational resources about TBI. This information will also be explained during the consent process. In addition, if a participant's status with respect to any of the study criteria change during the experiment (i.e., initiation of substance abuse), the participant's participation in the study may be terminated without their consent. Our consent form will include a statement regarding anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent and a statement indicating that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided.

Data collected from participants in this study will be shared with FITBIR Informatics System. The Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System is a central repository and resource for sharing data that was developed by the Department of Defense (DOD) and the National Institutes of Health (NIH) to promote collaboration, accelerate research, and advance knowledge on the characterization, prevention, diagnosis and treatment of traumatic brain injury (TBI). FITBIR provides a common platform and standardized format for data collection, retrieval and archiving, while allowing for flexibility in data entry and analysis. Additional information and detailed implementation guidance related to the FITBIR Informatics System can be found at http://fitbir.nih.gov (FITBIR Data Sharing Policy, 2017). All links to identifiers will be removed from the data before it is shared. Only de-identified data which does not include any direct identifiers that might directly identify you will be shared with FITBIR users and the general scientific community for research purposes (FITBIR Data Sharing Policy, 2017). Rakib Zaman (Rakib.zaman@publicissapient.com) is this study's contact at FITBIR Informatics Systems. His official title is "FITBIR Operations".

Statistical analyses will utilize the CTSC Biostatistics core. Power analyses and statistical analysis strategy were determined with our statistician Dr. Orrin Myers, who will continue to provide recommendations and support throughout the project. For Aim 1, the central analyses evaluate group (active vs. sham) differences in the MEG data and on the three Examiner composite variables across the three initial time points (before, immediately after, and 1 month after tDCS stimulation protocol). To test this hypothesis, three separate linear mixed models analyses will be performed using the three Examiner composite scores (Fluency, Cognitive Control, Working Memory) as dependent variables. In each analysis, we will incorporate three covariates that may predict variation in learning (depression: BDI score, premorbid intelligence: WTAR score, and symptom burden: NSI). This will allow us to determine predictors of treatment response. Sex, ethnicity, and age will also be entered into the statistical model. The effects of these covariates will be estimated by constructing appropriate contrasts in model effects. A similar set of analyses will evaluate group differences on the variables assessed in our long-term oral/phone follow-up (five data points: (1) before tDCS, (2) immediately after tDCS, (3) 1 month, (4) 3 months, and (5) 6 months. For these analyses dependent variables will be the total sensory items score of the NSI). Significant effects will be followed up with more fine-grained analysis of the components of composite scores. The use of linear mixed-models minimizes the adverse impact of a missing data point, which may well occur in a longitudinal clinical study such as this. Expected attrition will be taken into account with an intention-to-treat analysis. Missing data patterns will be analyzed to assess the extent to which they are informative (in contrast to missing at random), and analyses adjusted accordingly. All MEG data will undergo standard preprocessing (e.g. motion correction, spatial normalization) and quality control prior to statistical modeling. Depending on the specific question of the study, data may be analyzed using the general linear model, independent components analysis, machine learning techniques, or a variety of other standard approaches for neuroimaging data.

Data will be stored in Excel spreadsheet form as well as on hard copies.

Digital data will be stored on secure encrypted drives located behind a secure firewall. Data will be reviewed by the PI for quality control.

No data will be collected, transmitted, and/or stored via the internet. No data will be collected via audio/digital recordings. No data will be collected on video recordings or via photographs. Data will be stored for the duration of the study and will be destroyed after the final data analysis is complete. It will be stored at the Clinical Core on secured encrypted drives (digital) and in locked file cabinets behind locked doors in a secure area of the Clinical Core.

A Certificate of Confidentiality (CoC) has been received for this study. The CoC helps the researchers to protect the privacy of the subjects enrolled in the study from compulsory legal demands, such as court orders and subpoenas, for identifying information or identifying characteristics of a subject. This study is eligible for a CoC because it will collect personally identifiable, sensitive information about subjects, and will be federally funded. Sensitive information in this study includes information about a subject's neuropsychological performance and emotional states. This is information that if released could be damaging to a subject's financial standing, employability, or reputation within the community; pertains to a subject's psychological well-being or mental health; and might lead to social stigmatization or discrimination if it were disclosed.

17. Data and Specimen Banking

N/A

18. Risks to Subjects

Participation in this study for mild TBI subjects may involve minor risks and/or discomforts associated with possible breach of confidentiality risk, neuropsychological testing, sensory testing, MRI, and MEG.

MRI: Radio and magnetic waves associated with MRI scans are not associated with any known adverse effects. MRI is non-invasive and considered minimal risk by the FDA and OHRP. However, the scanner is a large magnet, so it could move objects containing ferrous metal in the room during the scan. All control and mmTBI participants are screened using the MRI safety screening form prior to be being scanned. Participants with any MRI scanning contraindications will be excluded from study participation. Participants may be bothered by feelings of claustrophobia (uncommon). The MRI also makes loud 'drum' beating noises during the study. There is a small risk that the MRI procedure may increase anxiety for participants who have post-traumatic stress disorder, Headphones are provided for protection. Rarely, large tattoos can heat up during an MRI scan and cause skin irritation like a sunburn (uncommon). No long-term harmful effects from MRI are known. However, since the effect of MRI on early development of the fetus is unknown, participants who are pregnant will not be allowed to go in the MRI. Females 18 years of age or older who suspect they may be pregnant will be asked to take a urine pregnancy test before being allowed to participate in the study. The test results will only be shared with participant.

MEG: The laboratory stimuli used in the current experiments are neither physically nor emotionally intense. The MEG recording procedures involve no pain or invasive techniques. The primary risk to the subjects during the MEG exam is discomfort from sitting still for approximately 90 minutes, or due to discomfort from electrodes on the scalp of the head or on the skin of the face. MEG itself is entirely noninvasive and only measures the signals naturally being generated by the activity in one's brain. There are no known health risks associated with the proposed MEG studies. A two-way intercom system and a video monitoring system provide continual monitoring of the subject's condition. If discomfort or concern is expressed or detected, the experiment will be stopped and the subject will be given the option to discontinue at any time.

Neuropsychological tests. The neuropsychological tasks involved in the protocol entail no foreseeable risk, besides perhaps fatigue or mild to moderate demands on attention and cognition. These are typically very marginally significant risks, mitigated by the fact that if a patient fatigues during testing they are given a rest break or are rescheduled. There is also mild psychological risk inherent in testing participants for cognitive abilities.

One potential risk is breach of confidentiality related to collection of sensitive information. Confidentiality issues are significant since this study collects a variety of sensitive data, in particular with respect to substance use. Because personal information is gathered, there exists the risk of possible invasion of privacy. However, our hard copy data is stored in locked cabinets in locked rooms within a locked, security-patrolled building; and there has never been a breach of confidentiality in our lab. Hence we believe that the likelihood of invasion of privacy is minimal.

Sensory testing: Participants may experience mild "motion sickness" or headache while using the virtual reality goggles to assess oculomotor control. Some participants may experience nausea, vomiting, or increased headache when performing sensory testing.

MEG: There is a very small possibility that participants with sensitive skin (e.g., contact dermatitis) may experience some skin irritation from the gel or sensors used for monitoring heartbeat and eye movements. (uncommon). There may be fatigue or restlessness associated with undergoing MEG. Subjects will be allowed to take breaks as needed during scanning.

Special Precautions
Subjects will be asked about any changes to medications or use of recreational substances or changes in eating/drinking habits at each assessment point. At study enrollment subjects will be asked to keep their medication use constant between the assessments, unless changes are medically recommended during that time, and that they should alert study personnel to any changes in their medications during the study period. Subjects will be asked not to smoke cigarettes or drink coffee 1 hour prior to arrival for testing, and that they should bring any and all assistive devices or wearable prosthetics with them to study appointments, including hearing aids, glasses, contact lenses. Women of child-bearing age will be asked to use two forms of contraception between pre- and post-stimulation assessment for pregnancy prevention. Subjects will be advised to avoid further head injuries while enrolled in the study, and to notify study personnel of any new injuries or other medical symptoms.

No special care or special equipment is needed for the subjects to be enrolled in the study.

Safety of stimulation (Visits #3-12).
A Data Safety and Monitoring Board (DSMB) will review study data with the PI quarterly for any side effects or adverse events. There are several risks associated with HD-tDCS treatment and sham procedures, however, based on our experience with this technology (3 current IRB-approved studies at UNM ongoing) we believe that these risks are minimal (Bikson et al, 2016). Common expectable side effects during HD-tDCS include skin redness, itching sensation, mild fatigue or drowsiness, nausea, and headache.

All patients undergoing stimulation with HD-tDCS will be asked to rate their discomfort with these symptoms every ten minutes, and the treatment will be stopped if discomfort rises above 7 on a 10-point anchored Likert scale, if mood is lowered to a rating of 2 or less, or at any time the patient wishes to stop. All efforts will be made to reduce subject discomfort and avoid the rare occurrence of skin burns, including evidence-based techniques such as using gel with HD-tDCS electrodes; offering emollient cream for reddened areas following stimulation; cleaning all electrodes regularly; not stimulating over skin with lesions or dermatologic conditions; checking skin impedance before stimulation. When these precautions are followed with conventional HD-tDCS protocols (i.e., 1-2 mA stimulation for up to 30 minutes), using optimized safety protocols, significant adverse effects, such as

burns on the skin near electrode affixation or heating of the electrodes affecting nearby scalp surface have not been reported.

In HD-tDCS, small circular electrodes with conductive gel are used to administer the current, which protects the scalp from irritation. Additionally, since more than two electrodes are used less current passes through each electrode, making slightly higher (e.g., 2mA) current strengths more comfortable. Multiple studies of HD-tDCS in patients with chronic pain, stroke, and tinnitus have demonstrated no differences in heart rate, blood pressure, or participant ratings of discomfort during treatments, no increased sensations compared to conventional sponge tDCS, and no adverse events. (Shekhawat et al, 2016, Richardson et al, 2015, Castillo-Saavedra et al, 2016)

Precautions taken in this study include monitoring mood with visual analog scales during stimulation, and pre/post-treatment depressive symptom questionnaires. There has not been a reported instance of suicidality caused by tDCS. In healthy controls there have been no reported adverse events of HD-tDCS, other than the physical sensations and skin irritation above. Of critical importance is the safety of HD-tDCS in patients with neurological illnesses that may carry some increased vulnerability to either brain damage or seizures. The experimental threshold at which tDCS causes brain injury was found to be two orders of magnitude above the current densities used in humans, making stimulation at the scalp with contemporary protocols causing brain damage extremely unlikely. tDCS is used in post-stroke patients in protocols that place the stimulating electrodes ipsilateral to the lesion and very often close to perilesional areas, without any increased side effects or adverse consequences (Richardson et al, 2015). Even more reassuring, tDCS at 1.0-2.0 mA has been performed over damaged left frontal cortex in 37 patients with moderate to severe TBIs, who are at the highest risk of post-traumatic seizures and demonstrate the greatest levels of structural damage, without adverse events, seizures, or decrements in neurologic status.(Li et al, 2016) A review of and contact with studies registered in clinicaltrials.gov for tDCS in TBI (Spaulding, NYU, U. Leige) did not discover any occurrence of seizures or adverse events.

COVID-19 Study Precautions

Study procedures may be amended based on UNMHSC, HRPO, state public health office, or federal regulations to minimize risk of infection. The following safety measures may be performed when appropriate:

- When possible, assessments that can be completed without research staff support may be sent to the participant to complete offsite (see Section 12)
- Participant screening will continue to be completed by phone.
- Prior to each participant visit and upon arrival at a visit, a research staff member may call or text prior to the scheduled participant visit or ask participant upon arrival questions to assess for COVID-19 symptoms. The "Participant COVID Symptom Checklist" will be used to assess for such symptoms. If any symptoms are endorsed, the PI will be notified, and the participant visit may be cancelled.
- Prior to arriving at work, staff may be required to complete the "Staff COVID Symptom Checklist". If any symptoms are endorsed, the PI will be notified, and the staff member may not work onsite until symptoms have resolved.
- During in-person research visits, the following precautions may be taken:
    - Social distancing (6')
    - Reducing the number of people in an exam room to no greater than 2 at a time
    - Include a barrier between research personnel and participants when 6' social distancing is not possible (i.e., assessments that requires close observation).
    - Minimize the number of staff who have "hands on" contact with study participants
    - Wearing personnel protective equipment (PPE) including gloves and masks.
    - Washing hands before and after contact with participants

- Disinfect surfaces and equipment in the location of the visit before and after each participant visit with recommended products from the EPA List N for approved disinfectants against SARS-CoV-2.

Li S et al. Clinical utility of brain stimulation modalities following traumatic brain injury: current evidence. Neuropsychiatric Disease and Treatment 2015; 11: 1573-1586.

Bikson M et al. Safety of transcranial direct current stimulation: evidence based update 2016.

Richardson J et al. Feasibility of using high-definition transcranial direct current stimulation (HD-tDCS) to enhance treatment outcomes in persons with aphasia. Neurorehabilitation 2015; 36: 115-126.

Shekhawat GS et al. Intensity, duration, and location of high-definition transcranial direct current stimulation for tinnitus relief. Neurorehabilitation and Neural Repair 2016; 30(4): 349-359.

Castillo-Saavedra L et al. Clinically effective treatment of fibromyalgia pain with high-definition transcranial direct current stimulation: phase 2 open-label dose optimization. The Journal of Pain 2016; 17: 14-26.

19. Potential Benefits to Subjects

There may be a mild temporary improvement in sensory symptoms as a result of participation in this study. This study has the potential to increase scientific understanding of the extent to which TBI-related sensory deficits can be modified with brain stimulation using a longitudinal design. Participants will receive a radiology review and report of their MRI scan and will be compensated for their time and inconvenience. No other direct benefit to participants is anticipated.

20. Recruitment Methods

The following groups will be recruited via the following methods:

1) Civilians healthy controls and TBI subjects: by distributed flyers, referrals from clinicians, and word of mouth. (overseen by UNM IRB)
2) Military healthy controls: by distributed flyers, referrals from clinicians, and word of mouth (overseen by NMVAHCS IRB)
3) Military TBI subjects: Human participants ages 18-69 who are enrolled in the NMVAHCS part of the study are automatically invited to come to the UNM CBRR to ask questions prior to providing consent.

Consent forms will be provided, as well as forms that again describe the study procedures and potential risks in detail. If potential participants are unsure about participation, they will be given a copy of the consent form with our contact information and be invited to call if they decide to participate. Once informed consent is obtained and the appropriate forms signed, the complete procedures of the study, as described in the consent forms, are provided to prospective subjects. We review the forms, and file them away in a locked file cabinet in a locked office at CBRR, away from any material with personal or sensitive study data. The participant will be assigned a unique research subject identifier (URSI) number, and from that point forward all research data will only be labeled

with the URSI number.

Randomization will occur at time of consenting. Once group membership is determined, individual participants will be scheduled for demographic data collection, neuropsychological assessments, MRI, MEG at UNM CBRR. Direct identifiers of participants will be maintained on a separate database that will be stored behind locked doors, in a locked filing cabinet in a secure area of the UNM CBRR, containing only the name, contact information, and address of the participants in order to send radiology reports to them, and perform followup telephone calls as needed.

21. Provisions to Protect the Privacy Interests of Subjects

No personally identifying information will be coded on the questionnaires, neuropsychological measures, brain imaging data, or any other data recording instruments, assuring confidentiality to the best of our ability. Subject identification numbers are assigned to each participant. Only the PI and HIPAA-trained project coordinator have access to the file that links names with subject numbers. Additionally, private health information may also be disclosed to DOD representatives including the research monitors and representatives of the DOD are authorized to review research records as a part of research oversight. All data are stored in locked file cabinets in a locked office, and on password-protected computers located behind a secure and maintained firewall until the time of study completion, or as long as the participant has agreed to have identifying information held for the purposes of future studies.

All data are collected by the PI, or trained research assistants who have completed on-line training in human subjects' research, HIPAA and research integrity; who are trained in our lab on research data management and confidentiality; and who are trained to criteria on project protocol. Data will be collected specifically for this proposed research project.

Specially designated interview rooms will be used for the purposes of obtaining consent, conducting research, and debriefing subjects. These rooms will be behind locked facility doors to which only the PI and trained research assistants will have access, ensuring privacy of the study participants.

22. Economic Burden to Subjects

Research Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
Demographic Assessment	2	x	
Neuropsychological/Sensory Testing	2	x	
Telephone Interviews	3	x	
MEG testing	2	x	
MRI	2	x	
Intervention	10	x	
_____	_____		
_____	_____		
Standard of Care Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
_____	_____		
_____	_____		

_____	_____		
_____	_____		
_____	_____		
_____	_____		
_____	_____		
_____	_____		

Participants will be responsible for travel to and from the testing site. Participants will not be charged for the costs of an investigational drug or device or intervention. Participants will be responsible for paying for treatment of adverse events. As numerous studies have documented minimal risk of adverse events for MRI, MEG, HD-tDCS, and neuropsychological testing with appropriate screening measures, any adverse events requiring medical care will be extremely unlikely. If incidental findings from the study result in the need for further evaluation/treatment, the participant or their insurance company will be responsible for additional clinical evaluation/treatment that may be needed. Also, incidental finding information is disclosed only to the individual participant. However, if a participant chooses to disclose such information also to their personal physician, this may become part of their medical record which may or may not have an effect in the future on getting health or life insurance.

23. Compensation

Each of the 40 healthy control participants will receive the equivalent of $100 for the first visit (Baseline Day 1) and $100 for the second visit (Baseline Day 2).

Each of the 80 mTBI participants will receive the equivalent of $100 for the first visit (Baseline Day 1), $100 for the second visit (Baseline Day 2), $100 for completing the 3rd visit (Post-Stimulation Day 1), $100 for completing the 4th visit (Post-Stimulation Day 2), and $60 for completing 3 follow-up visits. TBI participants will receive $100 for completing the first 5 intervention visits and $100 for completing the second 5 intervention visits. The maximum amount to be paid for involvement in the study is $660. Military participants who complete their follow-up visits at the VA will receive compensation for these followups via the VA system. This averages out to approximately $20 per hour. Subjects will be reimbursed in the form of merchandise cards dispersed in-person or sent to their email for taking part in the study at UNM. This is felt to be a fair amount that is not coercive and will help decrease attrition for this study that involves several visits. If subjects withdraw from the study early, they will be compensated for any sessions completed until the time of withdrawal.

Per 24 USC 30, payment to Federal Employees and Active Duty military personnel for participation in research while on duty is limited. Active Duty military personnel may not receive any other payment or non-monetary compensation for participation in a research study unless they are off duty or on leave during the time they are participating in the protocol.

24. Compensation for Research-Related Injury

Any medical care required by participants for injuries incurred during the research study will be performed at cost to the participant. All participants will be given information during the consent interview and provided at any time during the study regarding how to access urgent and emergency care at UNM, including emergency psychiatric care at UNM PES. These facilities are within 5-10 minute walk to the MIND Research Network Domenici Hall where the study facilities are located, and may also be accessed easily via emergency medical rescue (ie. 911 EMS).

25. Consent Process

Consent will be obtained by the PI, the research coordinator, or a research assistant. All persons obtaining consent will be trained and certified in the ethical treatment of human participants in research studies as taught in IRB-required courses.

In regards to screening for pregnancy, female subjects will be asked if they are pregnant, not pregnant, or not sure. If a woman says she is pregnant, she will be excluded from the study. All women of childbearing age will be required to have a negative pregnancy test to be enrolled. If enrolled she will be advised to use two forms of birth control during the time of the stimulation phase of the study. If she is not able or willing to take the pregnancy test, she will be excluded from the study.
If a patient remains interested and eligible, the project will be described in great details and the potential participant and their caregivers will be invited to ask questions prior to providing consent. If the participant is willing, they will be invited to schedule an appointment to undergo informed consent prior to study initiation. Appointments will be held at the Clinical Core in designed interview rooms behind secure facility doors so as to ensure privacy. Consent forms will be provided, as well as forms that again describe the study procedures and potential risks in detail. If potential participants are unsure about participation, they will be given a copy of the consent form with our contact information and be invited to call if they decide to participate. Once informed consent is obtained and the appropriate forms signed, the complete procedures of the study, as described in the consent forms, are provided to prospective subjects. We review the forms, and file them away in a locked file cabinet in a locked office, away from any material with personal or sensitive study data. Participants may withdraw their consent at any time during the study. At each study encounter participants are reminded that they have the ability to withdraw consent at any time.

All subjects will be asked whether they have the ability to consent themselves, or whether they have a legally authorized representative (LAR) available to make decisions with regard to informed consent for them. In such cases, patients with a LAR will be excluded from participation.

The process of determining whether an individual is capable of consent will take place after the study has been explained, but before the subject is asked to sign the consent form. A short list of questions regarding the purpose of the research, the research intervention, the clinical trial structure, the risks and benefits of the study, and the voluntary nature of it will be given to the subject before signing the consent form, to ensure capacity to understand and comprehend the study. Each subject must answer 100% of the "Consent Form Quiz" questions correctly; if answers are ambiguous or unclear the research team member will prompt the subject to clarify their meaning. If any questions are not answered correctly, the research team member will remind the subject of the pertinent information, and then ask the question(s) again. This will be repeated up to 2 times. If the subject still fails to answer the questions 100% appropriately after the third attempt, they may be invited back to undergo the consent process again on a different day. If after a second consent process the subject still cannot answer the questions 100% correctly, that subject will be excluded from the study.

If public health conditions require in-person research encounters be minimized some of the outlined consent procedures may be conducted over the phone. The following outlines phone consent procedures:

Military and healthy control participants (ages 18-69) enrolled in the study protocol at the NMVAHCS will automatically be called so that they can ask questions prior to providing consent (for UNM part of protocol). After discussing the study and asking questions, potential participants who complete screening and are eligible for participation, will be mailed or emailed the consent form that describes the study procedures and potential risks in great detail. Participants will be given our contact information and be invited to call if they decide to participate. If they decide to participate, a consent phone call will be conducted in which the consent form is reviewed, the participant can ask questions,

and if interested in continuing participation, the Consent Form Quiz will be completed (over the phone). If they are successful with the quiz, they will be scheduled for their first visit. Consent form signature will be done in person, at their first visit, so that it can be witnessed and signed by research staff. Once informed consent is obtained and the appropriate forms signed, the participant will be assigned a unique research subject identifier (URSI) number, and from that point forward all research data will only be labeled with the URSI number. The key linking identifiers of participants to the URSI will be maintained on a separate database that will be stored behind locked doors, in a locked filing cabinet in a secure area of the CBRR, and on the UNMHSC secure server.

The participants will be reminded at each study encounter that they have the ability to withdraw consent at any time to protect against loss of capacity to consent. It is highly unlikely that there will be any deterioration in decisional capacity as a result of the study procedures themselves, as they exert no direct effect on the brain. Given that subjects will only have mild TBIs, with chronic symptoms, it is also unlikely that they will lose decisional capacity spontaneously during the course of the study. However, should study staff or the PI suspect a change in capacity due to new inability to follow the protocol, the subject will be assessed, and undergo re-consent if appropriate.

26. Documentation of Consent (see attached forms)

27. Study Test Results/Incidental Findings (see next section)

28. Sharing Study Progress or Results with Subjects

As the neuropsychological and MEG tests employed in the study are for research purposes and not diagnostic purposes, these results will not be shared with the participants, unless their physician requests to see a report. In this instance the Clinical Core will obtain the participant's permission to generate a summary report of the neuropsychological test results and send this to the participant's primary care physician. Subjects will not be provided with summaries of trial progress, or summaries of study results.

All research MRI scans are read for incidental findings by a radiologist. A report is sent by mail to the participant. When the scan is read, an e-mail notification is sent to the participant letting them know new results are available. The participant can securely log in to the COINS Homepage to access their MRI radiology report. No sensitive or identifying information is sent via e-mail. If an abnormality that requires follow-up is identified, such as a Doctor Referral recommendation, a hard copy of the report may be mailed to the participant in addition to the e-mail notification. In these cases, the MRN Medical Director may also attempt to contact the participant by phone to explain the information and help answer questions.

29. Inclusion of Vulnerable Populations

There will be no gender restrictions with regard to sample inclusion. It is expected that our sample will reflect a mix of national sample characteristics of military TBI populations (approximately 95% male and 5% female) and civilian TBI populations (approximately 55% male and 45% female). The age range of 18-69 years was selected because we did not want to include developmental processes in our analyses and by 18 years old, many major neurodevelopmental changes in the brain will have taken place. Using similar logic, we chose to include participants up to the age of 69 because we do not want to include advancing age-related changes in our analyses. It is expected that the sample included in this study will reflect the demographics of the greater Albuquerque metropolitan community. The racial composition of the community is 69.7% White, 2.47% African American, 5.53% Native American, 1.64% Asian, 0.10% Pacific Islander, 16.37% from other races, and 4.15% from two or more races. Hispanic or Latino people of any race were 41.48% of the population. Through randomization, we will ensure that the sample obtained represents the study population. Adults unable to consent,

individuals who are not yet adults (infants, children, teenagers), pregnant women, and prisoners will be excluded from the study.

The compensation for participation in the study is calibrated so as not to exert undue influence on economically disadvantaged participants. The materials, instructions, consents, and scripts involved in the study will be geared toward a low-enough educational level that the majority of educationally disadvantaged participants will be able to understand them.

Recruitment will be unrestricted with regard to minorities, with the exception that non-English reading/speaking-only individuals will not be eligible. Albuquerque's population is multicultural, with a particularly large representation of Hispanic (mostly Mexican American) people. Ethnicity, Hispanic or other, will be determined through self-identification. In compliance with NIH policy participants will be asked to self identify as to Hispanic or Non-Hispanic as well as American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. All possible combinations of the multiple responses will be reported.

30. Community-Based Participatory Research N/A

31. Research Involving American Indian/Native Populations N/A

32. Transnational Research N/A

33. Drugs or Devices

During testing sessions, subjects will be engaging in sensory tasks. One of the tasks will be delivered using a commercially available head-mounted virtual reality device, Oculus Rift DK. This device will be outfiitted with eye-tracking sensors to quantify subject's eye movements in response to the vision therapy, so as to assess symptom reduction (iscan.com). Because these devices simply display images and record eye movements, without imparting any energy into the head or body, they are nonsignificant risk. The only potential side effect of use of the Oculus Rift is mild nausea.

During intervention sessions, subjects will receive HD-tDCS while performing sensory training tasks on a computer.

The HD-tDCS device is determined to be a Non-Significant Risk device by the sponsor-investigator (Davin Quinn, MD) for the following reasons:

1) It is not intended as an implant.
2) It does not present a potential for serious risk to the health, safety, or welfare of the subjects.
3) It is not proposed to be for use in supporting or sustaining human life.
4) It is not of substantial importance in diagnosing, curing, mitigating, or treating disease, or preventing impairment of human health.

According to the FDA, serious adverse events are those in which the outcome is death, life-threatening, hospitalization, disability/permanent damage, congenital anomaly, requiring intervention to prevent permanent impairment, or other serious events such as refractory seizures, cardiorespiratory arrest, or anaphylactic reaction. No serious adverse events attributable to HD-tDCS have been reported in the more than 10,000 subjects investigated in the contemporary tDCS literature since 1998. This literature includes studies in patients with severe brain injury, stroke, epilepsy, and neurodegenerative disorders, none of whom have been reported to experience serious adverse events. Specifically, there have been no reports or evidence presented of damage to the brain, seizures, or cardiorespiratory arrest. Animal studies of charge densities necessary to induce brain damage in rats were found to be 100 times higher than the charge density used in TDCS trials with standard parameters (< 2.5 mA, no

more than 2 sessions daily, < 60 min per session, use of electrodes that minimize skin burns) as determined by world-wide expert consensus. As this trial will be operating within standard parameters as defined above, we believe our use of HD-tDCS in subjects with mild traumatic brain injury represents a Non-Significant Risk. Even more reassuring, tDCS at 1.0-2.0 mA has been performed over damaged left frontal cortex in 37 patients with moderate to severe TBIs, who are at the highest risk of post-traumatic seizures and demonstrate the greatest levels of structural damage, without adverse events, seizures, or decrements in neurologic status.(Li et al, 2016) A review of and contact with studies registered in clinicaltrials.gov for tDCS in TBI (Spaulding, NYU, U. Leige) did not discover any occurrence of seizures or adverse events.
Furthermore, the Soterix MxN device has already been deemed a Non-Significant Risk device by the UNM HSC HRRC in several studies, one involving neurologically damaged patients (Study #16-091, "Targeted transcranial direct current stimulation (tDCS) to Enhance Speech-Language Treatment Outcomes in Persons with Chronic Post Stroke Aphasia; Study #16-328, "Real-time measurement of cortical hemodynamics during concurrent brain stimulation and cognitive tasks.

Given that our patient population is an outpatient, ambulatory, mild TBI population and that these current strengths and amounts have already been administered safely to patients with stroke lesions ipsilateral and proximal to the site of stimulation, we feel that HD-tDCS is extremely safe. Our group is currently studying HD-tDCS in subjects with stroke and healthy controls and are have found the stimulation to be very safe and well tolerated. There are no long-term neuropsychiatric effects from HD-tDCS. With repeated stimulation, some subjects get dry skin. Applying lotion helps to ameliorate this. Using EEG gel for the electrode conductor helps reduce this occurrence as well. The commonly reported side effects of HD-tDCS are itching, burning, tingling, headache, and discomfort (10-40%), all of which are mild and transient. A few people in other studies have experienced drowsiness, excitement, or dizziness after HD-tDCS.

As with any contact between persons and electrical apparatuses, there is a slight possibility of electrical shock. To our knowledge, no studies have reported any electrical shock resulting from HD-tDCS, and we do not expect this event to occur in our experiment.

34. Checklist Section

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

I. Waivers or Alterations of Consent, Assent, and HIPAA Authorization

A. Partial Waiver of Consent for Screening/Recruitment

Complete this checklist if you are requesting a partial waiver of consent so that you can review private information to identify potential subjects and/or determine eligibility prior to approaching potential subjects for consent or parental permission.

1. Describe the data source that you need to review (e.g., medical records):
2. Describe the purpose for the review (e.g., screening):
3. Describe who will conducting the reviews (e.g., investigators, research staff):
4. Do all persons who will be conducting the reviews already have permitted access to the data source?

   ☐ Yes

   ☐ No. Explain:

5. Verify that each of the following are true or provide an alternate justification for the underlined regulatory criteria:

   a) <u>The activity involves no more than minimal risk to the subjects</u> because the records review itself is non-invasive and the results of the records review will not be used for any purposes other than those described above.

      ☐ True

      ☐ Other justification:

   b) <u>The waiver or alteration will not adversely affect the rights and welfare of the subjects</u> because eligible subjects will be approached for consent to participate in the research and are free to decline. Further, the information accessed during the records review will not be disclosed to anyone without a legitimate purpose (e.g., verification of eligibility).

      ☐ True

      ☐ Other justification:

c) The research could not practicably be carried out without the waiver or alteration because there is no other reasonably efficient and effective way to identify who to approach for possible participation in the research.

☐ True

☐ Other justification:

d) Whenever appropriate, potentially eligible subjects will be presented with information about the research and asked to consider participation. *(Regulatory criteria: Whenever appropriate, the subjects will be provided with additional pertinent information after participation.)*

☐ True

☐ Other justification:

Partial Waiver of HIPAA Authorization for Screening/Recruitment

Complete the following additional questions/attestations if the records you will review to identify potential subjects and/or determine eligibility include Protected Health Information (PHI).

6. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?

   ☐ Yes. Describe:

   ☐ No

7. If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained:

8. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☐ True

   ☐ False

B. Waiver of Documentation of Consent

Complete this checklist if you intend to obtain consent verbally but will not be obtaining signatures from subjects on a consent form to document consent. Waivers

of documentation of consent are commonly requested when using scripts, information sheets, or email or survey introductions to present the elements of consent instead of using a traditional consent form.

1. Are you requesting a waiver of documentation of consent for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Provide justification for <u>one</u> of the following:

   a) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

   b) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

3. Do you intend to provide subjects with a written statement regarding the research in lieu of a traditional consent form?

   ☐ Yes. Please attach a copy to your submission in Click.

   ☐ No

C. Alteration of Consent

Complete this checklist if you intend to obtain consent but will be eliminating or altering one or more of the required elements of consent. Alterations of consent are commonly requested for research involving deception or for minimal risk research when an abbreviated consent is desired and one or more of the required element are not relevant to the research.

<u>Note: FDA-regulated research is not eligible for an alteration of consent.</u>

1. Which element(s) of consent do you wish to eliminate <u>and</u> why?

2. Which element(s) of consent do you wish to alter <u>and</u> why?

3. Provide justification for each of the following regulatory criteria:
    a) The research involves no more than minimal risk to the subjects:

    b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

    c) The research could not practicably be carried out without the waiver or alteration:

    d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

D. Full Waiver of Consent/Parental Permission

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of consent are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

Note: FDA-regulated research is not eligible for a full waiver of consent using these criteria. If you believe that your FDA-regulated research may be eligible for a waiver under another mechanism, such as planned emergency research, contact the HRPO for assistance in determining what information to provide to the HRRC.

1. Are you requesting a waiver for some or all subjects?
    ☐ All
    ☐ Some. Explain:

2. Provide justification for each of the following regulatory criteria:
    a) The research involves no more than minimal risk to the subjects:

    b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

    c) The research could not practicably be carried out without the waiver or alteration:

d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

E. Full Waiver of Consent/Parental Permission (Public Benefit or Service Programs)

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort) and the research involves the evaluation of a public benefit or service program.

1. Are you requesting a waiver for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Provide justification for each of the following regulatory criteria:

   a) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs:

   b) The research could not practicably be carried out without the waiver or alteration.

F. Full Waiver of HIPAA Authorization

Complete this checklist if you are requesting a full waiver of the requirement to obtain HIPAA authorization for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of HIPAA authorization are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

1. Are you requesting a waiver of authorization for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Describe your plan to protect health information identifiers from improper use and disclosure:

3. Describe your plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so):

4. Describe why the research could not practicably be conducted without the waiver or alteration:

5. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☐ True

   ☐ False

G. Other Waiver Types

If you are seeking another waiver type (e.g., Planned Emergency Research, Waiver of Parental Permission to Protect Child Participants, Enforcement Discretion for In Vitro Diagnostics, etc. contact the HRPO office for assistance in determining what information to submit for the HRRC's consideration.

II. Vulnerable Populations

A. Adults with Cognitive Impairments

Complete this checklist if the subject population will include adults with cognitive impairments.

This checklist does not need to be completed if the research doesn't involve interactions or interventions with subjects and will be conducted under a waiver of consent.

1. Describe why the objectives of the study cannot be met without inclusion of adults with cognitive impairments.

Traumatic brain injury results in a set of well-known postconcussive symptoms, that include difficulties with memory and attention. Therefore, in order to study a treatment for postconcussive symptoms, a population of subjects with TBI must be enrolled, and these subjects may have cognitive impairments.

2. Describe how capacity to consent will be evaluated.

A consent quiz covering key aspects of the study will be administered after explanation of the consent form, but before signing. Participants must answer all questions on the quiz correctly in order to be permitted to enroll in the study. They will receive two opportunities to correct any incorrect answers. If after two opportunities the subject still cannot answer the question correctly, the subject will not be enrolled.

3. If subjects may regain capacity to consent, or if subjects may have fluctuating capacity to consent, describe your plans to evaluate capacity to consent throughout the research and to obtain consent to continue participation if capacity is regained.

All subjects will be re-evaluated for capacity to consent by study staff if there is reason to suspect a loss of capacity, such as new inability to perform the study tasks. If capacity to re-consent is not present, the subject will be dropped from the study, and all necessary measures taken to refer the subject to appropriate medical care, such as referral to a physician, or transport to an emergency department. However, given that all subjects will have only mild traumatic brain injuries, that are chronic in nature, it is highly unlikely that a subject will lose capacity to consent during the course of the study.

4. Describe your plans, if any, to provide information about the research to subjects and the steps you will take to assess understanding.

Subjects will be provided with the consent, and the protocol, if requested, to read before undergoing informed consent. Capacity to provide informed consent will be assessed for every patient entering the study. This includes a quiz that assess understanding of the nature of the project, its status as research, and the voluntary nature of the subject's participation.

5. Describe your plans to obtain assent, including whether assent will be obtained from none, some, or all subjects.

As subjects must be able to give their own informed consent to be in the study, and no subjects with legally appointed guardians will be allowed to enter the study, assent will not be obtained.

6. Describe why risks to subjects are reasonable in relation to anticipated benefits to the subjects.

There are only nonsignificant risks associated with the procedures of this study, which include neuropsychological testing, demographic assessment, and brain imaging. Therefore the risk to

subjects is miniscule and is not disproportionate to the minimal benefit anticipated for subjects in this study (having a brain scan performed).

7. If this study involves a health or behavioral intervention, describe why the relation of the anticipated benefit to the risk of the research is at least as favorable to the subjects as that presented by alternative procedures.

In this protocol at UNM there is no health or behavioral intervention.

8. Describe your plans for monitoring the well-being of subjects including any plans to withdraw subjects from the research if they appear to be unduly distressed.

At every study visit subjects will be asked if they are still willing to be in the study. Every study visit involves collection of data that pertains to their mental state, and thus study staff will be well aware if any subject is unduly distressed. In these circumstances, if a subject is unduly distressed, they will be offered the opportunity to stop the study procedures, or to speak to a study staff member, or to drop out of the study entirely. If in need of referral or immediate medical assistance, the study staff will ensure the subject receives the appropriate level of care for their distress.

B. Children

Complete this checklist if the subject population will include children.

1. Select the category of research that you believe this research falls within and provide justification for any associated criteria. If there are different assessments for different groups of children or arms (e.g., placebo vs. drug), include a memo to provide an assessment for each group.

☐ Research not involving greater than minimal risk. *(Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.)*

☐ Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

Provide justification for each of the following criteria:

(1) The risk is justified by the anticipated benefit to the subjects:

(2) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches:

☐ Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

Provide justification for each of the following criteria:

(1) The risk represents a minor increase over minimal risk:

(2) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations:

(3) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition

C. Pregnant Women and Fetuses

Complete this checklist if the subject population will include pregnant women and fetuses.

This checklist does not need to be completed if the research is both minimal risk and is not conducted, funded, or otherwise subject to regulation by DHHS, DOD, EPA, or VA.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; ***or***, if there is no such prospect of benefit, the risk to the fetus is not greater than

minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

3. Any risk is the least possible for achieving the objectives of the research.

D. Neonates of Uncertain Viability or Nonviable Neonates

Complete this checklist if the subject population will include neonates of uncertain viability.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, ***or***, the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research

E. Nonviable Neonates

Complete this checklist if the subject population will include nonviable neonates.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

Verify each of the following:

5. Vital functions of the neonate will not be artificially maintained

   ☐ True

   ☐ False

6. The research will not terminate the heartbeat or respiration of the neonate

   ☐ True

   ☐ False

7. There will be no added risk to the neonate resulting from the research

   ☐ True

   ☐ False

F. Biomedical and Behavioral Research Involving Prisoners

Complete this checklist if the subject population will include prisoners.

Note: Minimal risk for research involving prisoners is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

1. Select and justify which allowable category of research involving prisoners this research falls within:

   ☐ Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

☐ Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

☐ Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults)

☐ Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject

☐ Epidemiologic studies in which the sole purpose is to describe the prevalence or incidence of a disease by identifying all cases or to study potential risk factor associations for a disease, the research presents no more than Minimal Risk and no more than inconvenience to the subjects, and Prisoners are not a particular focus of the research.

2. Provide justification for each of the following regulatory criteria:

   a) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired

   b) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers

   c) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless justification is provided, control subjects must be selected randomly from the group of available

prisoners who meet the characteristics needed for that particular research project

d) The information is presented in language which is understandable to the subject population

e) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole

f) When appropriate, adequate provision has been made for follow up examination or care after research participation, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact

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III. Medical Devices

Complete this checklist if the research evaluates the safety or effectiveness of a medical device. If more than one medical device is being evaluated, provide the requested information for each.

A. Device Name: MxN multichannel transcranial electrical stimulator

B. Manufacturer: Soterix Medical, Inc.

C. Does the research involve a Significant Risk Device under an IDE?

☐ Yes. Include documentation of the FDA approval of the IDE with your submission. *Acceptable methods of documentation include: (1) FDA letter noting IDE number and approval status; (2) Industry sponsor letter noting IDE number and FDA approval status; or (3) FDA-approved industry sponsor protocol with IDE number noted*

☒ No

D. Is the research IDE-exempt?

☐ Yes. Include a FDA letter with your submission noting the determination that the research is IDE-exempt or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is IDE-exempt*.

☒ No

E. Does the research involve a Non-Significant Risk (NSR) Device?

☒ Yes. Include a FDA letter with your submission noting the determination that the research is NSR or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is NSR**.

☐ No

* This FDA guidance includes a description for when a device study is exempt from the IDE requirements: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf

**This FDA guidance includes information on how to differentiate between Significant Risk and Non-Significant Risk device studies: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

Appendix A

DSMB Personnel and Duties

Christopher Abbott, MD
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Sarah Pirio Richardson, MD
Associate Professor: Neurology Adult
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Summary of Duties: Will participate in quarterly DSMB meetings to act in an advisory capacity to the study team to monitor participant safety and data quality and evaluate the progress of the study. They will serve in an individual capacity and provide expertise and recommendations. As a part of the DSMB, they will be responsible for safeguarding the interests of trial participants, for assessing the safety of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. They will provide recommendations about stopping or continuing the trial and may also formulate recommendations relating to the selection/recruitment/retention of participants, their management, adherence to protocol specified-regimens, and procedures for data management and quality control. As members of this DSMB, they will have a further responsibility to consider the interests of research subjects whose therapy may ultimately be influenced by trial results.

Authorities: Shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report.
Responsibilities: Shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

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