PROTOCOL TITLE:

Transcranial direct current stimulation for treatment of deficits after traumatic brain injury.

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1. Objectives

Our long-term goal is to develop safe and effective treatments for symptoms of mild to moderate TBI (mmTBI) that restore patients to higher levels of functioning, decrease disability, and promote brain healing. The objective of this application is to investigate the use of transcranial direct current stimulation (tDCS) to treat symptoms of executive dysfunction and depression in patients with mmTBI. Our central hypotheses are (1) tDCS paired with relevant cognitive training facilitates improves executive function on NIH-approved neuropsychological measures, (2) tDCS reduces depression scores on NIH Common Data Elements for TBI, (3) that these improvements in emotion and cognition will be detectable up to one year after stimulation, (4) (4) certain clinical variables will reliably predict response to tDCS, such as age, education level, injury severity, and magnetic resonance imaging (MRI) evidence of structural/functional/metabolic abnormalities and (5) quantitative electroencephalography (EEG) will demonstrate changes in frontal midline theta band power and theta band synchrony, markers of cognitive control, in responders. These objectives were formulated based on our clinical experience with Dr. Ronald Yeo (project mentor) characterizing symptomatic patients with mmTBI in the post-acute setting, groundbreaking research led by Dr. Vincent Clark (project mentor) that has demonstrated robust increases in attention and learning with tDCS, and extensive evidence accumulated by co-junior investigator on the grant application Dr. James Cavanagh on EEG measures of executive dysfunction.

Specific Aim 1: tDCS for executive dysfunction in mmTBI
Experiments in this aim will test the hypothesis that in patients with mmTBI, left prefrontal anodal tDCS concurrent with cognitive training for up to ten consecutive weekdays will result in significantly more improvement in executive function compared to sham stimulation. Patients with cognitive complaints 3 months to 15 years after mmTBI will be recruited from local emergency departments and brain injury clinics. Healthy controls will also be recruited through flyers, advertisements and word of mouth. Aim 1.1: tDCS will be paired with computer-based cognitive training tasks of response inhibition, set shifting, and working memory, while executive function will be measured with the NIH Examiner battery before, immediately after, and one month after stimulation. Pre-and post-stimulation EEG and MRI may be obtained. During EEG and MRI participants may be asked to rest quietly or perform simple tasks. Aim 1.2: Persistence of post-traumatic symptom reduction and quality of life improvement will be assessed with Common Data Elements instruments via telephone interview at 6 months and one year. Aim 1.3: Clinical predictors of tDCS response including EEG frontal theta synchrony, injury severity, presence of neuroimaging abnormalities, premorbid intelligence, and post-traumatic symptom burden will be determined with linear mixed-models analysis.

Specific Aim 2: tDCS for depressive symptoms in mmTBI
Experiments in this aim will test the hypothesis that left prefrontal anodal tDCS in patients with mmTBI will significantly reduce depressive symptoms compared to sham stimulation. Aim 2.1: Patients will be assessed for symptoms of depression via self-report instruments and clinician-administered scales from NIH Common Data Elements before, immediately after, and one month after the stimulation protocol. Aim 2.2: Persistence of antidepressant benefit will be assessed via telephone interview at 6 months and one year. Aim 2.3: clinical predictors of tDCS response such as EEG frontal theta synchrony, injury severity, premorbid intelligence, neuroimaging abnormalities, and symptom burden will be determined.

2. Background

Traumatic brain injury (TBI) is a significant public health problem. An estimated 1.7 million TBI-related deaths, hospitalizations, and emergency department (ED) visits occur in the United States each year,[1] costing an estimated $76.5 billion in 2000 alone.[2] Among 34 states in a 2004 survey New Mexico had the 2nd highest TBI fatality rate, with approximately 10,000 ED visits and 1400 admissions for TBI, making this an important regional problem to be addressed for our communities.[3] Even after mild TBI, up to 22% of patients will report functional impairment at one year post-injury.[4] Much of this loss of function is due to the fact that the majority of TBIs affect the frontal lobes and cause damage to the frontal-subcortical circuits that are responsible for the complex thought processes required to navigate contemporary life,[5,6] including comportment and social behavior, mood and motivation, and especially cognitive control.[7]

These deficits in cognition and emotion compound one another, as the neural circuits mediating them are closely interconnected.[8,9] Within the first year after TBI 33% of patients will suffer a major depressive disorder,[10] which may exacerbate any separate post-traumatic cognitive deficits and effectively render a "double-hit" to patients' abilities to manage their lives' daily activities.[9] Conversely, deficits in the domain of cognitive control can be seen even after only mild TBIs,[11] affecting executive functions such as response inhibition, working memory impairment, and set shifting and leading to further depression as patients spend long periods functionally disabled.[7,8] Unfortunately, few effective treatments exist for the post-acute neurobehavioral sequelae of TBI. Current strategies for cognitive rehabilitation are both time- and resource intensive but yield only small effect sizes.[12] Non-FDA approved treatments such as methylphenidate are coarse in their mechanism of action and carry adverse consequences such as irritability, addiction, and cardiovascular effects.[13] Dopamine agonists have had mixed results in improving function after TBI,[14,15] and little evidence currently exists to recommend any other class of medication.[16] Treatment approaches for mood symptoms in TBI are understudied, nonspecific, and have even been shown to worsen cognition.[17,18] Novel rehabilitation approaches that simultaneously and holistically address both the cognitive and emotional post-traumatic deficits of TBI are needed.

The current proposal represents a major step towards a solution for post-TBI symptoms that harnesses the intact brain's neuroplastic potential to overcome a variety of deficits. Transcranial direct current stimulation (tDCS) is a non-invasive form of brain stimulation utilizing low amounts of current to modulate neuronal activity and improve neuropsychiatric symptoms across diverse disorders, including post-stroke aphasia and motor learning, working memory in dementia, and major depression.[19,20–22] We will attempt to demonstrate that tDCS produces similar gains in cognitive symptoms among mmTBI patients as we have seen in our lab,[23] as well as improvements in depressive symptoms others have found in depressed patients.[19] We will then correlate response to tDCS with EEG measures of cognitive control and brain connectivity so as to better identify patients likely to benefit from tDCS, as well as clarify the mechanism of therapeutic action of tDCS. Due to its low cost, minimal side effects, and the ease with which it can be integrated with existing rehabilitation approaches, empirical support for tDCS would be a "game-changer" in the field of TBI. Successful completion of our specific aims will have a major impact on research and clinical practice regarding the management of debilitating TBI symptoms. Toxic effects of medications could be avoided; visits to rehabilitation facilities could be reduced; and treatment could be provided in diverse settings. Future studies would elucidate optimal electrode placements and stimulation parameters for specific cognitive symptoms and in specific types of brain injury, as well as provide a rational mechanism of therapeutic action in terms of improved functional brain connectivity. Integration with emerging multimodal neuroimaging techniques may reveal exactly which type of patient benefits from which type of tDCS, personalizing clinical interventions.

Review of relevant literature

tDCS can improve brain function. Anodal tDCS typically has an excitatory neuronal effect due to a shift toward depolarization, while cathodal stimulation elicits a hyperpolarization.[24] tDCS-induced changes last from minutes to hours, and multiple stimulation sessions over the course of days to weeks can lead to cumulative long-lasting effects.[25–27] This powerful neuroplastic effect of tDCS has

already been applied to injured brain in patients recovering from stroke, with observed benefits in motor control, neglect, vision, and aphasia, without adverse consequences such as seizures or worsening of deficits.[27,28,29,30] Anodal stimulation of the dorsolateral prefrontal cortex (DLPFC) has become a standard protocol in the cognitive tDCS literature because of its ability to improve multiple dimensions of cognitive functioning,[31–33] including cognitive control and working memory,[31,32,34,] attention,[35] improved decision making,[36] and enhanced memory.[37] Reduction of impulsivity has been demonstrated with anode over right DLPFC.[38,39]

tDCS is understudied in TBI. Application of this therapy to TBI is a logical next step, but tDCS has not been extensively studied in this disorder as it has for stroke rehabilitation and depression.[19,40] Several animal studies have shown that anodal tDCS is potentially neuroprotective after brain injury.[41,42] Only three studies have attempted tDCS for cognition in TBI, all utilizing left prefrontal anodal stimulation. Angelakis et al. treated 5 severe TBI patients with 5 days of anodal 1 mA tDCS for 20 minutes then 5 days of 2 mA. Age of injury ranged from 6 months to 10 years, and electrode positioning was at left DLPFC or left sensorimotor cortex (C3) in alternating order. There were no adverse events, and no clear advantage from either electrode position. Three patients of the five experienced benefit by 1 year followup.

Kang et al, in a one-session protocol[43] involving 9 patients with moderate-severe TBI 2-18 months from date of injury, administered 2mA tDCS for 20 minutes while they performed a computerized cognitive rehabilitation program. Significant benefits in set-switching and reaction time were detected immediately after and up to 24 hours later. There were no adverse events and the treatment was well tolerated, despite all subjects having known left frontal lobe pathology. In contrast, Lesniak et al. administered tDCS at 1 mA for 10 minutes to 23 TBI patients for fifteen sessions over a 3-week protocol. All patients had severe TBI between 4 and 92 months from date of injury, 16 of whom had known left frontal pathology. Their group found the treatments safe and well tolerated, but failed to find any significant benefit in a multitude of attentional domains.[44] Our correspondence with studies registered in clinicaltrials.gov for tDCS in TBI (Spaulding, NYU, U. Leige) did not discover any occurrence of seizures or serious adverse events.

We conclude the following from these studies: (1) anodal tDCS over left DLPFC at various current densities, durations, and over multiple sessions in TBI patients of moderate and severe degree is safe; (2) the presence of pre-treatment brain abnormalities, even at the site of anodal electrode, does not necessarily increase risk nor impede benefit, and (3) the severity of injury and current density/stimulation protocol used may influence the efficacy of tDCS.

Choice of study population. Our research strategy is focused on the mild to moderate range of TBI severity. Importantly, this range of severity captures the vast majority of TBI patients. Though we believe patients with severe injuries may also benefit from tDCS, we are concerned that their greater burden of neuropathology may compromise plasticity.[44] Our research strategy calls for patients to be beyond the acute phase of injury with a minimum of a three-month period since injury. Our clinical experience suggests that patients are medically stable at this time but often struggling with persisting cognitive and emotional sequelae of mmTBI. By applying the technique in patients with mild to moderate severity the likelihood of intact neural circuits undergoing a robust adaptive neuroplastic change is maximized. An ongoing controversy in the TBI literature is the high rate of postconcussive symptoms that occur in healthy non-TBI populations, calling into question the validity of these symptoms. By simultaneously recruiting healthy controls as a comparator group, we will be able to demonstrate that there are clear cognitive control deficits in mmTBI patients, and whether tDCS is more or less efficacious in a clinical versus nonclinical population.

tDCS is effective in clinical studies at UNM. Our group at UNM has experimented with a number of different variables regarding tDCS to determine optimal effects on attention and learning.[23] Using a paradigm of a threat detection task for learning, Clark and colleagues found activation on fMRI in right inferior frontal cortex and right parietal cortex, which were then used as targets for stimulation.

Higher current densities, up to 2 mA for 30 minutes, applied to these localized networks produced greater increases in learning on the threat detection task in a dose-response manner that were still detectable one hour later (Figure 2). Using the same paradigm, we then demonstrated a prolonged effect on alerting attention with the Attention Network Task after just one 30 minute session of anodal tDCS to right inferior frontal cortex.[45] Variables that most enhanced task performance were exposure to task stimuli during stimulation and repetition of the various stimulus response contingencies. Therefore there is ample experience at our center to conduct intensive studies of tDCS for mmTBI and to determine optimal stimulation paradigms and patient characteristics. In addition, the PI of the current project has written several reviews of safety of neuromodulation therapies in various patient populations and treated hundreds of clinical patients with electrical stimulation.[46,47]

Established expertise in neuroimaging of TBI. Our group has also been very active in the longitudinal study of TBI patients, utilizing multimodal neuroimaging and neuropsychological testing to assess biomarkers of injury and recovery.[48,49] In adult and pediatric mTBI populations we have documented deficits in attention,[50] post-traumatic symptoms,[48] diffusion tensor abnormalities,[51] neurometabolites,[49] and fMRI differences,[52] both in the semi-acute phase and in the chronic phase (4 months post-injury). We have used fMRI to examine attentional dysfunction in patients with TBI, observing decreased activation in both sub-cortical and cortical networks. The PI of this project has been providing clinical care for brain injured patients on an inpatient neurosurgical service and in an outpatient neuropsychiatry clinic for the past five years, and has ample experience with retention, characterization, and treatment of this clinical population.[53,54] MRI sequences for characterization of TBI may be obtained as part of baseline and post-stimulation assessment in a subgroup of mmTBI subjects. The advantage of obtaining neuroimaging in this study is three-fold: 1) structural abnormalities may affect current flow and alter the effectiveness of TDCS; 2) TDCS has been shown by our group to increase glutamate under the anodal electrode, and use of MRS to characterize neurometabolite flux before and after stimulation could add important evidence to this theory; 3) mmTBI may cause functional brain activation abnormalities independent of structural lesions that can be correlated and localized with EEG.

EEG is a candidate biomarker for tDCS effect in TBI. Co-Junior investigator Cavanagh has extensive experience analyzing EEG measures of frontal midline theta band synchrony in various populations as a phenomenon underlying cognitive control.[55,56] Task-related EEG abnormalities have been found to distinguish patients with mmTBI from healthy controls, and correlate with executive dysfunction.[57,58] PI Cavanagh's co-occurring study will investigate whether functional EEG variables such as theta band phase synchrony will correlate with the common disturbances of cognitive control during the semi-acute stage of recovery from mmTBI. We will apply this technique to investigate whether chronic post-concussive symptoms are associated with these same EEG abnormalities, and what effect tDCS may have to increase frontal theta synchrony.

3. Study Design

This study is a randomized placebo-controlled clinical trial. Investigators will be blinded to the type of stimulation given (sham versus active) through use of a computer-assisted pre-programmed tDCS stimulator. Subjects will be blinded to sham versus active through the use of low-current (up to 0.2 mA) sham stimulation, which provides a tactile sensation similar to active 2.0 mA stimulation. Ramping up and down the current at the beginning of stimulation also prevents subjects from distinguishing sham from active. The duration of an individual subject's participation in the research may range up to 1 year. The duration anticipated to enroll all subjects is 3 to 4 years. The expected duration for the investigators to complete the study (complete analysis) is 5 years.

Inclusion and Exclusion Criteria
Human participants who have suffered mmTBI (ages 18-55) will be recruited from the UNM Hospital ED and from other local Emergency Departments via CTSC patient recruitment services. Healthy controls will be recruited from the greater Albuquerque area via flyers and online ads. If a participant shows interest in participating in our study, a brief prescreening will be done over the telephone prior to initiating informed consent procedures. The prescreening procedures will assure that each potential participant meets study inclusion and exclusion criteria. If, after prescreening, the patient remains interested and eligible, the project will be described in great details and the potential participant and their caregivers will be invited to come to the investigation site 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, away from any material with personal or sensitive study data.

Inclusion Criteria
Patients seen the emergency department (ED) will be enrolled in this study if they 1) are aged 18-55, 2) have suffered a TBI with documented evidence of loss of consciousness (LOC) which was less than 24 hours, 3) were injured between 3 months and 15 years ago, 4) received a Glasgow coma scale (GCS) score of between 9 and 15 upon ED admission, 5) experienced less than 1 week of post-traumatic amnesia (PTA), and 6) have post-traumatic cognitive symptoms as evidenced by endorsing at least 1 out of 4 cognitive symptoms on the Neurobehavioral Symptom Inventory (NSI), a measure of post-traumatic symptoms from the NIH Common Data Elements, and 7) have been on stable doses of any psychotropic medications for the past 2 months.. Healthy controls will be between the ages of 18-55.

Exclusion Criteria
Potential participants will be excluded from participation in this study if there is 1) a prior history of other neurological disease or any history of seizures, 2) history of psychosis 3) history of current or recent (within two years) substance/alcohol dependence, 4) any discontinuity in skull electrical conductivity (i.e., unhealed burr holes in scalp) or artificially constructed (metal or plastic) craniotomy cover; 5) presence of any implanted electrical device (e.g. pacemaker), 6) recent medical instability (within three weeks), 7) any condition that would prevent the subject from completing the protocol, 8) appointment of a legal representative, as assessed via direct inquiry of the subject and a designated trusted other. Because our population will have only mild to moderate TBIs, and be well beyond the subacute phase of injury (> 3 months), ongoing complications from the injury itself such as skin infection, bleeding, ischemia, swelling, increased intracranial pressure, seizures, and hyponatremia will be extremely unlikely. However, these would be considered exclusionary criteria if present over the previous three weeks prior to enrollment. Adults unable to consent, individuals who are not yet adults (infants, children, teenagers), pregnant women, and prisoners are specifically excluded from the study. Persons not fluent in English will be excluded, as the neuropsychological test batteries are administered in English.

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	26	38	64
Not Hispanic or Latino	38	58	96
Ethnic Category: Total of All Subjects *	64	96	160
Racial Categories			
American Indian/Alaska Native	4	4	8
Asian	2	2	4
Pacific Islander	2	2	4
Black or African American	2	2	4
White	46	66	112
Other races	10	16	26
Two or more races	2	4	6
Racial Categories: Total of All Subjects *	64	96	160

4. Study Timelines

GOAL	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5
Project Progress	Human Subjects Review Board approval completed Equipment purchased Biostatistical training completed Clinical Supervisor and Research Assistant training completed Begin participant recruitment (targeted enrollment of 10 active tDCS patients and 10 controls) Progress reported to Human Research Protections Office (HRPO), PI, and NIH.	Recruited 20 active tDCS patients and 20 controls Preliminary data analyses on tDCS effects completed, in preparation for NIH grant submission Progress reports submitted to to HRPO, PI and NIH	Recruited 10 active tDCS patients and 10 controls Completed preliminary data analyses of group differences in tDCS effects across groups Progress reports submitted to to HRPO, PI and NIH	Progress reports submitted to to HRPO, PI and NIH Complete all data analysis	Progress reports submitted to to HRPO, PI and NIH Closure Report submitted to HRPO

5. Study Endpoints

Primary endpoint: change in scores on the EXAMINER battery from before to after stimulation.

Secondary endpoints: change in score on the Neurobehavioral Symptom Inventory, Beck Depression Inventory-II, Hamilton Rating Scale for Depression, change in frontal midline theta synchrony on EEG, change in MRI abnormalities, and quality of life measure from time 0 to 1 year.

6. Research Setting

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

Subjects will be identified and recruited from the UNM ED and other local EDs via the CTSC patient recruitment service, as well as coordination with ED providers and posted advertisements. Healthy controls will be recruited through online advertisements, word of mouth and flyers. As the only Level 1 trauma center for the state of New Mexico and the community hospital for Bernalillo County and the city of Albuquerque, which is the most populous city in the state, UNM treats the majority of TBIs presenting in the state. Approximately 10,000 New Mexicans receive treatment for a TBI in hospitals annually, and the majority of these injuries (~9000) are mild in nature; therefore, recruiting 80 TBI subjects and 80 healthy controls over 3 years is felt to be a feasible goal.

7. 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 will study the administration of transcranial direct current stimulation to patients with mild to moderate traumatic brain injury (TBI) to ameliorate chronic cognitive and emotional deficits, and 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 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.

During this same period Dr. Quinn has become involved in brain stimulation therapies, at first through their important role in the treatment of the catatonic syndrome, on which he has published several reviews and case reports. 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 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. Of his mentors, Dr. Vince Clark is an expert in transcranial direct current stimulation, its mechanisms of action, and its use to enhance cognition, and will provide key guidance regarding the application of this neurostimulatory technology. Dr. Ronald Yeo is a prolific researcher in the neuropsychology and neuroimaging of TBI, and will provide methodological and research design expertise. Additional guidance will be provided by Dr. Richard Campbell, who as part of the Clinical Core will be a resource for pragmatics of neuropsychological assessment, and Dr. Andrew Mayer, who is also expert in neuroimaging of TBI and methodological issues.

Facilities/Resources of the UNM Center for Brain Recovery and Repair

Traumatic brain injuries are a common clinical disorder treated at UNM. Approximately 10,000 New Mexicans seek treatment for a TBI each year. As UNM is the only Level 1 trauma center in the region and is situated in the largest city in the state with a metropolitan catchment area population of 1 million, a large percentage of the TBIs sustained in New Mexico are treated at UNM. The majority of TBIs are mTBI, with approximately 1000 New Mexicans each year hospitalized with TBI and 9000 mild enough to be treated in the outpatient setting. Therefore, we expect that if 1/10 of New Mexicans with mTBIs present to UNM each year, that equates to 900 mTBIs eligible for screening. We plan to screen these patients and recruit approximately 25-30 annually for the study, meaning that we are aiming to enroll 3% of eligible patients, which we believe is feasible.

Clinical Study Coordinator—In Year 1, a clinical study coordinator will be hired to support junior principal investigators' research projects. The study coordinator will be responsible for the coordination and administration of clinical studies under the direction of the Core co-directors. The clinical study coordinator will help develop, implement, and coordinate research and administrative procedures for the successful management of clinical studies; be responsible for scheduling neuropsychological assessments, neuroimaging appointments, and treatment appointments; and will also be responsible for scheduling regular Core group meetings.

Research Technician—In year 1, two technicians will be hired to assist in the junior PI's projects. We will assign one research technician to each of the initial junior PI projects. Their effort will be dedicated to assist in recruitment/screening, neuropsychological assessment administration, scoring and summary report preparation, scheduling of treatments and neuroimaging procedures, as well as data entry of collected data. Research technicians will be made available to assist with other future junior PI projects and pilot projects.

Technicians, research coordinators, and the investigators will undergo standard training in human research standards, ethics, conflict of interest, and also participate in weekly research group meetings regarding the specific protocol being studied, methodological and analytical issues, and subject recruitment, participation, and safety.

Transcranial Direct Current Stimulation (tDCS)—A tDCS system (neuroConn: DC-Stimulator PLUS) will be purchased in Year 1, with a second added in Year 2. 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. Transcranial stimulation using weak electric currents over a period of several minutes is demonstrated to modify neuronal excitability and circuit function and can serve to provide long-lasting promotion of brain recovery and repair.

Neuropsychological Assessment Measures. The Core will establish a library of advanced neuropsychological tools, applicable to assessment of different aspects of recovery and repair following stroke or TBI. The library will be useful for subjects of different ages and severity of injury. This library will include 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 will also develop and maintain an instrument bank of health-outcome measures, including state-of-the-art, computer-administered measures.

1) *National Institutes of Health Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (EXAMINER)*. EXAMINER is battery of reliable and valid tests of executive function developed under the auspices of the NINDS for clinical investigations and is adaptable across a wide range of ages and disorders (www.examiner.ucsf.edu).

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.

3) *Patient Reported Outcomes Measurement Information System (PROMIS®).* The PROMIS®, is a system of highly reliable, precise measures of patient–reported (both child and adult) health status for physical, mental, and social well–being and can be useful in measuring effectiveness of treatment in clinical intervention studies.

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 investigators with scheduling of assessments, neuroimaging, and treatment appointments. The Core will provide space for interventions being studied as part of research projects. 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 REDCap, a web-based electronic data capture program that is secure and HIPAA compliant available through the UNM CTSC Biomedical Informatics (http://hsc.unm.edu/research/ctsc/BMI/REDCap.shtml). Neuropsychological data will be entered by psychometrists into study databases with accuracy verified by double using UNM Health Sciences Center Library Services to create a data management plan to manage and provide access of research data collected in line with current NIH policies.

3T MRI is housed immediately proximal to the neuropsychological testing rooms, as part of the MIND Research Network (MRN) advanced biomedical imaging 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 MIND Research Network and can provide basic to advanced care 24 hours a day, 7 days a week.

8. Prior Approvals

Departmental Approval form included.

9. Multi-Site Research NA

10.Study Procedures

Specific Aim 1.1: Acute effectiveness of tDCS in mmTBI

Experimental Design and Methods

Participants: Eighty TBI subjects will be recruited for this study, all having suffered mild or moderate TBI (mmTBI, as defined before) at least 3 months prior to study enrollment, but not more than 15 years prior to enrollment. 80 age- and sex-matched healthy controls will be recruited. All participants will be 18-55 years of age. We will expect to screen approximately 120 patients with mmTBI in order to reach our goal of 80 TBI subjects. The experimental pre-post, double-blind design is graphically displayed. It includes randomization of TBI patients to either a left-sided active transcranial direct current stimulation (tDCS) protocol, or sham treatment group to foster isolation and identification of any tDCS treatment effects. To enhance our statistical power to identify predictors of treatment response in mmTBI patients, 40 TBI subjects and 40 controls will be assigned to each group: left-sham and left-active.

Recruitment: Recruitment primarily will be through the UNM Hospital Emergency Department (ED) (the only Level 1 trauma center in New Mexico). The UNM Health Sciences Center (HSC) Clinical and Translational Science Center (CTSC) Participant Recruitment Service (PRS) for Clinical Research will monitor ED intake records for patients who meet criteria once released from the hospital, then notify the study team of these cases. A second means of recruitment will involve direct referrals from UNM and non-UNM ED physicians and/or referrals from any clinic in the Albuquerque metropolitan area, via the distribution of flyers and calls to clinical directors to publicize the study. A third means of recruitment will involve information listed on the UNM CBRR and MRN websites, and posted flyers.

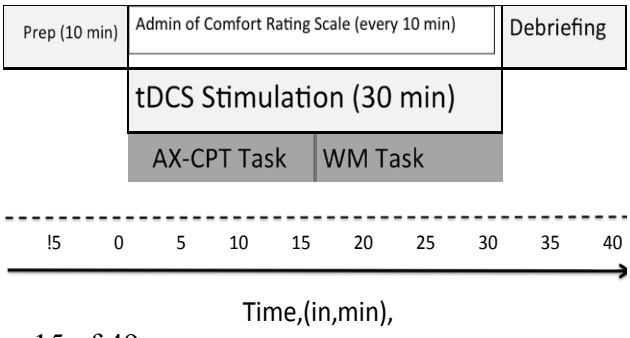
Subjects who meet initial criteria for inclusion will be contacted by a member of the research team and invited to enroll in the study. Interested patients will be invited to the offices of the Center for Brain Recovery and Repair clinical core for formal screening procedures. A brief structured interview will be administered along with the NSI. If potential participants do not meet study criteria, they will be thanked for their time and identifying information recorded for future reference. Subjects with a legally authorized representative (LAR) will be excluded from the study, and all participants will be screened for LAR. All participants will be adults (ages 18-55), and all participants will consent for themselves. Although participants will be recruited from referral or from emergency department (or other) records, no participant will be enrolled in the study without being given sufficient opportunity to consider whether or not to participate. In most cases, they will undergo multiple interactions with study personnel over the course of days, and during each they will have the opportunity to ask questions and discuss their decision to participate. They will have multiple opportunities to reconsider any decisions during the screening and consent process, minimizing the possibility of coercion or undue influence by the researchers. If potential participants successfully meet basic study criteria, they will be invited to undergo consent procedures and enrolled in the study. All participants will be fluent in English, and the information contained in the consent form will be discussed with them in addition to their having a written description of the study in the form, to assure that they truly understand the study procedures.

Randomization will occur at time of consenting. The study coordinator who consented the patient will use a coin-tossing procedure to determine whether the subject is assigned to the active group (group 1) or control group (group 2). Modifications will be made as necessary toward the end of enrollment to ensure equal group size and balanced distribution of demographic variables such as age and gender. The study coordinator will not be blinded to group assignment, and with the assistance of the Clinical Core, will program the TDCS devices to deliver active or sham stimulation depending on which group the subject has been assigned. However, the coordinator will not be involved in performing any stimulation procedures. The study technician and principle investigator, who will be responsible for administering the stimulation, will not be aware of which group receives active versus control, and will thus be blinded, as the TDCS device will only display the group number (1 or 2).

Once group membership is determined, individual participants may undergo demographic data collection, neuropsychological assessments and tDCS treatment sessions. They may also undergo EEG and/or MRI. 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 Clinical Core.

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, 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.

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 variables to be studied are the three composite scores generated by



the Examiner battery (e.g. Cognitive Control, Fluency, and Working Memory). The following domains and tests will be administered: Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (Examiner); Digit Span; Delis-Kaplan Executive Function Systems (DKEFS) Trailmaking Test Conditions 2 and 4; Hopkins Verbal Learning Test (HVLT); Frontal Systems Behavior Scale (FrSBe); Test of Memory Malingering (TOMM); Wechsler Test of Adult Reading (WTAR); Digit Symbol Coding; Handedness; Socioeconomic Status (SES); Neurobehavioral Symptom Inventory (NSI); PROMIS-29 profile; Glasgow Outcome Scale-Extended (GOSE).

Resting and task-related electroencephalography: Electroencephalograph (EEG) may be done after neuropsychological testing in a subset of subjects. The participant will wear a cap during the EEG to record brain waves. EEG setup takes between 10 and 30 minutes, and subsequent recording takes one to two hours. During EEG assessments participants will complete numerous active tasks. Each task is designed to parse different cognitive mechanisms that contribute to adaptive performance. In perceptual tasks, participants will discriminate tone pitches amongst novel distracting tones. In decision making tasks, participants are required to classify stimuli based on pre-determined types of rules. For learning tasks, participants are asked to select among two or more pictures on the screen by pressing a button on the keyboard or gamepad, they are then presented with a reward ('+1') or not ('0) following their choice. For memory tasks, participants will view stimuli one at a time on the computer screen, and will be probed on their memory of these stimuli after a short delay. Some tasks alter the fidelity of the stimuli to make decisions more difficult, others alter the perceptual-motor mappings to make response selection more difficult, and others simply probe risk and reward preferences.

Magnetic resonance imaging: MRI scan(s) will involve simultaneous functional or cognitive tasks, including sequences assessing diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), functional MRI (fMRI), and structural sequences. Total scan time, including participant setup and removal, is expected to take 1.5 hours. Based on the study by Gasparovic et al in 2009 examining MR spectroscopy in mild TBI, utilizing an effect size of 1.27, a planned sample size of 30 subjects receiving MRI will achieve 80% power to detect a difference between groups. Participants may lie down on a table and be placed into a long donut-shaped magnet. During the scan, participants will be shown pictures and/or words and will be asked to make decisions about the information presented in them. No contrast will be used. Any female over 18 who thinks she may be pregnant 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 tDCS Intervention: On the same day as assessment or the next day, participants will receive either active left anodal tDCS for a total of 30 minutes or sham for an equivalent duration, each day for up to ten consecutive weekdays. Current will be ramped up over 1 minute at initiation and ramped down over 1 minute with termination.

A NeuroConn tDCS (investigational) machine will be used to administer tDCS current. Targeting of the left DLPFC (F3 position, International 10-20 system of EEG coordinates) may be done by (1) locating the vertex (Cz) at the midpoint of the nasion-inion line and the midpoint of the preauricular-preauricular line; (2) locating M1 at 20% of the Cz-preauricular distance, measured from Cz; (3) locating F3 5 centimeters anterior to M1 in the horizontal plane. This method has been shown to be suitable for tDCS electrode targeting of left DLPFC.[59] The Beam F3 method may also be used, which yields equivalent or better accuracy. Square-shaped solution-soaked or gel-soaked sponge electrodes, held by a rubber casing, are applied to the scalp using elastic bandage material. The anode will be placed on the scalp over the F3 target location and the cathode placed on the right upper arm

below the deltoid. Current for the treatment condition will be applied at 2.0 mA for a total delivered charge of 60 mA-min.

Safety of stimulation. During tDCS application, subjects will describe physical sensations such as tingling or itching using a 10-point anchored Likert scale. Administration of tDCS will be stopped immediately if subjects report a 7 or above for discomfort, or if subjects wish to stop at any time. Subjects will also have their mood, energy, pain, and arousal levels assessed using visual analog 10-point scales. These checks will occur every ten minutes during the stimulation session.

Double blind design and sham treatment: The sham stimulation (control) group will receive up to 0.2 mA current for 30 minutes each session, with an initial ramping up and down of stimulation to mimic active stimulation. The sham current is used as a control condition, rather than the absence of stimulation, to equate aspects of the procedure (preparation and application of electrodes, attachment with adhesive strips, etc.), and to give the participant a degree of physical sensation that is somewhat similar to that of the 2.0 mA stimulation group while remaining well below the level sufficient to affect brain function and behavior.[60] To accomplish a double blind, the tDCS machine is programmed to randomize sham versus active stimulation and keeps track of the stimulation protocol for later downloading.

Cognitive control Tasks: Participants may be administered the cognitive training battery for 30 minutes, during treatment and sham. Session procedures will begin with tDCS electrode placement while seated in a comfortable chair. After initiation of tDCS, the cognitive training will be administered on a laboratory computer. The two tasks will be presented for 15 minutes each, in counterbalanced alternating order over the ten sessions. The tasks to be coupled with tDCS are the AX-CPT (set shifting/response inhibition) and a dual auditory/visual N-back task (working memory), and were selected based on their activation of the critical neural networks associated with the three executive functions of interest.[61–64] AX-CPT is a continuous performance task in which subjects must respond to specific paired letter combinations (A followed by X) with a button press while inhibiting response to non-target combinations (AY, BY, BX) (Figure 8). The dual N-back task is a continuous performance test in which subjects respond to simultaneous sequences of visuospatial and auditory stimuli being presented that match preceding stimuli n-steps earlier in the sequence.[65]

Specific Aim 1.2: Persistence of tDCS effects and quality of life

Experimental Design and Methods

Participants: TBI subjects enrolled in Aim 1.1 will be entered into a data registry with comprehensive contact information, including contact information (phone, email, fax, mail address) not just on participants, but also on multiple collaterals we can contact for 6 month and 1 year assessments.

Assessments: Initial screening will be done prior to tDCS intervention, and will be performed verbally to resemble subsequent phone interviews. These assessments will include the Neurobehavioral Symptom Inventory (NSI), and the PROMIS-29 quality of life profile. Dimensions queried by the PROMIS-29 survey will include physical function, anxiety, depression, fatigue, pain, sleep, and social roles. At 6 months and 1 year after the end of stimulation, subjects will be contacted by phone by the research team for a brief assessment of their post-traumatic symptoms and quality of life. Subjects not able to be contacted by phone will be sent a letter with the surveys in paper form to be returned via mail, fax, or email.

Specific Aim 1.3: Clinical predictors of tDCS response

Experimental Design and Methods

Participants: TBI subjects from Aim 1.1 will be carried forward for study in Aim 1.3. Key clinical variables in the study group will be analyzed for association with tDCS effect, namely, lesser post-traumatic symptom burden as measured by the NSI, mild versus moderate severity of TBI, lack of neuroimaging abnormalities on MRI, and higher premorbid level of intelligence as measured by the WTAR, as these are factors shown to predict better recovery from TBI.[44,66,67]

Specific Aim 2.1: Effectiveness of tDCS for depression after mmTBI

We will undertake an investigation of tDCS for depressed mood after mmTBI. The same protocol as for Aim 1 will be employed to investigate Aim 2, with a focus on depressive symptoms. The stimulation paradigm is similar to the regimen used by Brunoni et al. in their study comparing tDCS to sertraline for depression (10 sessions, 30 minutes/session). However, their paradigm is limited in its power to identify the therapeutic element of tDCS for depression, because it does not separate the effects of simultaneous anodal/cathodal influences. Our configuration with the cathode placed on the contralateral arm, developed and tested in our lab,[68] thereby ensures that only one type of neuromodulation is delivered to the brain, rather than two. Subjects receiving active anodal left prefrontal tDCS for ten days will experience significantly greater improvement in depressive symptoms compared to sham stimulation, as assessed with NIH Common Data Elements depression instruments, that will be detectable immediately after stimulation and at 1 month post-stimulation.

Experimental Design and Methods

Recruitment: Recruitment, enrollment, and data collection for Aim 2 will be identical to the experimental design of Aim 1. Subjects will be randomly assigned to active stimulation or sham stimulation groups.

Depression Assessments: As part of the neuropsychological test battery administered to the participants before, immediately after, and at 1 month after tDCS, subjects will be assessed for depressive symptoms using NIH Common Data Elements instruments as well as reliable and valid instruments for detecting mood disturbances in TBI populations. These tests are the Beck Depression Inventory (BDI-II),[69] and the Hamilton Rating Scale for Depression (HAM-D).[70] Post-traumatic stress disorder (PTSD) symptoms, which often predispose to depression after TBI, will be assessed using the PTSD Checklist (PCL).[71] These will be conducted verbally, so as to ensure similarity of delivery with the long-term assessments. Any patient who reports thoughts of death or suicidal ideation at any point during the stimulation protocol or assessments will be immediately evaluated by the PI and given appropriate emergency medical care at the UNM Psychiatric Emergency Service.

Stimulation Protocol: The protocol will be identical to the stimulation regimen described in Aim 1. During the procedure for each stimulation session, participants will be asked to rate their mood according to a 10-point visual analog scale before and after each stimulation session (10 sessions total). This will monitor for daily fluctuations in mood as well as any rare stimulation-related severe mood changes.

Specific Aim 2.2:
The subjects from Aim 2.1 will be automatically included. At 6 months and 1 year after stimulation, subjects will be contacted via telephone and administered the depression assessment tools utilized before, immediately after, and 1 month after stimulation.
Specific Aim 2.3: Subjects from Aim 2.1 will be carried forward for study in Aim 2.3. Patient and injury characteristics will predict positive response to tDCS, namely, higher premorbid intellectual function (WTAR), lesser severity of injury (mild versus moderate), lack of neuroimaging abnormalities on MRI, and more severe pre-stimulation depressive symptoms (BDI, HAM-D). Understanding which of the clinical variables described above moderate the efficacy of tDCS in mmTBI will allow for more precise patient selection and better overall efficacy in future applications.

Each of the 80 participants will receive $20/hr in the form of cash cards for taking part in the study.. This is felt to be a fair amount that is not coercive and will help decrease attrition for this study which involves many visits.

11.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. Yeo, and Hunter are skilled in analysis of the various MRI sequences and will assist the PI in analysis of the neuroimaging data.

Statistical analyses will utilize the CTSC Biostatistics core. Power analyses and statistical analysis strategy were determined with our statistician Dr. Ronald Schrader, who will continue to provide recommendations and support throughout the project. Sufficient group sizes were determined on the basis of data derived from preliminary studies. 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.[22] 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. Power in the linear mixed model analysis should be superior that that of the t-test. For Aim 1.1, the central analyses evaluate group (active vs. sham) differences in the EEG 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 (severity: mild vs. moderate, premorbid intelligence: WTAR score, and symptom burden: NSI). This will allow us to determine predictors of treatment response (Specific Aim 1.3). 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 post-tDCS, (4) 6 months, and (5) 1 year) for Aim 1.2. For these analyses dependent variables will be the total cognitive items score of the NSI and the PROMIS-29 profile total score). 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 EEG 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.

12. 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 Data Safety and Monitoring Board (DSMB) will review the study data on a quarterly basis with the PI to ensure participant safety. The DSMB for this study will be composed of Dr. Christopher Abbott, the medical director of the Electroconvulsive Therapy Service at UNM, and Dr. Jose Padin-Rosado, staff epileptologist of the Epilepsy Monitoring Unit at UNM. Their experience in assuring safety of brain stimulation therapies and seizure monitoring protocols make them ideally suited to serving on this project's DSMB. Continuous, close monitoring of participant safety will include prompt and frequent reporting of safety data (i.e., adverse/serious adverse events) to the

DMSB, the University of New Mexico Health Sciences Center Institutional Review Board (UNMHSC IRB) and/or appropriate NIH staff with oversight responsibility. The PI will provide a summary of the safe conduct of the study to NIH 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. 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.

13. Withdrawal of Subjects

During tDCS application, subjects will describe physical sensations such as tingling or itching using a 10-point anchored Likert scale. Administration of tDCS will be stopped immediately if subjects report a 7 or above for discomfort, or if subjects wish to stop at any time. Subjects will also have their mood, energy, pain, and arousal levels assessed using visual analog 10-point scales. These checks will occur every ten minutes during the stimulation session. Any report of pain or decreased level of arousal by the patient will result in stopping of stimulation.

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.

14. Data Management/Confidentiality

Neuropsychological testing and questions regarding depression, post-concussive symptoms, and quality of life will be collected from all participants. All forms of data described above will be recorded on to paper and pencil or computerized data forms that do not contain identifying information. A separate file contains contact information for the purpose of mailing the radiology review letter and future contact, in 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, on password-protected computers located behind a secure and maintained firewall. Data will also be collected and stored on a drive only accessible by the research team on a secure MRN server, and/or in the COINS database on an Amazon Web Services (AWS) HIPAA compliant cloud server. The cloud based server and any other electronic

storage is accessible only by the research team, and data is coded with the unique subject identification numbers.

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. MRN retains the link between identifiers and URSI indefinitely for the potential future benefit to the research participant. Specifically, it may become medically advantageous in the future for a former participant to have access to the clinical information that is present in most radiological scans. For example, if a participant is diagnosed with a neurological condition (e.g. multiple sclerosis, glioblastoma, TBI, etc.) it may be clinically beneficial for the participant's physician to have access to a research scan that was performed at an earlier time-point to determine disease course and severity.
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.

Statistical analyses will utilize the CTSC Biostatistics core. Power analyses and statistical analysis strategy were determined with our statistician Dr. Ronald Schrader, who will continue to provide recommendations and support throughout the project. For Aim 1.1, the central analyses evaluate group (active vs. sham) differences 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 (severity: mild vs. moderate, premorbid intelligence: WTAR score, and symptom burden: NSI). This will allow us to determine predictors of treatment response (Specific Aim 1.3). 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 post-tDCS, (4) 6 months, and (5) 1 year) for Aim 1.2. For these analyses dependent variables will be the total cognitive items score of the NSI and the PROMIS-29 profile total score). 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. 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.

Human subjects in the proposed protocol may receive screening and diagnostic interviews, phenotypic assessment (including emotional, cognitive and behavioral functioning), including interview and questionnaire queries regarding their mental health history, substance use history, and history of prior brain injuries and other neurological disease or injury. A link between identifiers and data be created; It will be stored separately in a locked file cabinet behind locked doors in a secure area of the Clinical Core for the duration of the study (5 years). It will be disposed of and shredded after the conclusion of the final data analysis. Only the PI and trained research personnel will have access to the data, and will be solely responsible for receipt or transmission of the data. 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 from the NIH once IRB approval is in place. 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.

15. Data and Specimen Banking (see section on Data Management)

16. Risks to Subjects

Participation in this study for both healthy controls and mmTBI subjects may involve minor risks and/or discomforts associated with possible breach of confidentiality risk, neuropsychological testing, MRI, EEG, and tDCS.

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. Headphones are provided for protection. Rarely, large or recent 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.

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.

EEG: There is a very small possibility that participants with sensitive skin (e.g., contact dermatitis) may experience some skin irritation from the EEG gel or metal sensor (uncommon).

tDCS. There are several risks associated with tDCS treatment and sham procedures, however, based on our experience with this technology (>500 research subjects run to date), we believe that these risks are minimal. Common expectable side effects during tDCS include skin redness, itching sensation, mild fatigue or drowsiness, nausea, and headache.[72] All patients undergoing stimulation with tDCS will be asked to rate their discomfort with these symptoms every ten minutes, and the treatment will be terminated if discomfort rises above 7 on a 10-point anchored Likert scale, 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 saline-soaked sponges with lower concentrations (~15mM) of solution; offering emollient cream for reddened areas following stimulation; preventing electrodes from drying out during stimulation; disinfecting all treatment sponges regularly; not stimulating over skin with lesions or dermatologic conditions; checking skin impedance before stimulation.[59,7374] When these precautions are followed with conventional 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.[75]

Rare mood changes with tDCS have been observed in studies of depressed patients, resulting in several cases of hypomania.[76,77] Most of these patients were taking concurrent antidepressants. Precautions taken in this study include excluding patients on psychotropic medications, and 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 TDCS, other than the physical sensations and skin irritation above. Of critical importance is the safety of 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.[78] tDCS is widely 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.[2040] 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.[43,44,79] 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.

Safeguard exclusions that the study will have in place are enumerated above, and will ensure that neurologically unstable patients are screened out of the study, or those who might be at higher risk from cranial electrical stimulation. A Data Safety and Monitoring Board composed of Dr. Christopher Abbott and Dr. Jose Padin-Rosado, specialists in neurostimulation and seizures respectively, will be meeting with the PI quarterly to review outcome data to ensure rigorous protection of patients, as described below.

17. Potential Benefits to Subjects

This study has the potential for providing mild transient benefits in cognition and mood for individual subjects. The probability for these improvements is moderate, given that multiple prospective blinded controlled studies have demonstrated transient improvements in cognition and mood for patients with strokes, neurodegenerative diseases, and in healthy controls. This study has the potential to increase scientific understanding of the extent to which TBI-related cognitive deficits can be remediated with tDCS 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.

18. Recruitment Methods

Recruitment primarily will be through the UNM Hospital Emergency Department (ED) (the only Level 1 trauma center in New Mexico). The UNM Health Sciences Center (HSC) Clinical and Translational Science Center (CTSC) Participant Recruitment Service (PRS) for Clinical Research will monitor ED intake records for patients who meet criteria once released from the hospital, then notify the study team of these cases. A second means of recruitment will involve direct referrals from UNM and non-UNM ED physicians and/or referrals from any clinic in the Albuquerque metropolitan area, via the distribution of flyers and calls to clinical directors to publicize the study. This will include referrals from the New Mexico VA Health Care System. Flyers for VA clinics will include disclaimer language required by the Veterans Administration and we will obtain a facility approval letter from the New Mexico VA. A third means of recruitment will involve information listed on the UNM CBRR and MRN websites. Patients who meet initial criteria for inclusion will be contacted by a member of the research team and invited to enroll in the study. Interested patients will be invited to the offices of the Center for Brain Recovery and Repair clinical core for formal screening procedures. A brief structured interview will be administered along with the NSI. If potential participants do not meet study criteria, they will be thanked for their time and identifying information recorded for future reference. Subjects with a legally authorized representative (LAR) will be excluded from the study, and all participants will be screened for LAR. All participants will be adults (ages 18-55), and all participants will consent for themselves. Although participants will be recruited from referral or from emergency department (or other) records, no participant will be enrolled in the study without being given sufficient opportunity to consider whether or not to participate. In most cases, they will undergo multiple interactions with study personnel over the course of days, and during each they will have the opportunity to ask questions and discuss their decision to participate. They will have

multiple opportunities to reconsider any decisions during the screening and consent process, minimizing the possibility of coercion or undue influence by the researchers. If potential participants successfully meet basic study criteria, they will be invited to undergo consent procedures and enrolled in the study. All participants will be fluent in English, and the information contained in the consent form will be discussed with them in addition to their having a written description of the study in the form, to assure that they truly understand the study procedures.

A modified repeated fair coin-tossing randomization procedure will determine group assignment, and modifications will be made as necessary toward the end of enrollment to ensure equal group size. Randomization will occur at time of consenting. The study coordinator who consented the patient will use a coin-tossing procedure to determine whether the subject is assigned to the active group (group 1) or control group (group 2). Modifications will be made as necessary toward the end of enrollment to ensure equal group size and balanced distribution of demographic variables such as age and gender. The study coordinator will not be blinded to group assignment, and with the assistance of the Clinical Core, will program the TDCS devices to deliver active or sham stimulation depending on which group the subject has been assigned. However, the coordinator will not be involved in performing any stimulation procedures. The study technician and principle investigator, who will be responsible for administering the stimulation, will not be aware of which group receives active versus control, and will thus be blinded, as the TDCS device will only display the group number (1 or 2).

Once group membership is determined, individual participants will be scheduled for demographic data collection, neuropsychological assessments, EEG, and tDCS treatment sessions. 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 Clinical Core.

19.Provisions to Protect the Privacy Interests of Subjects

Neuropsychological testing and questions regarding depression, post-concussive symptoms, and quality of life will be collected from all participants. All forms of data described above will be recorded on to paper and pencil or computerized data forms that do not contain identifying information. A separate file contains contact information 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 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.

20. Economic Burden to Subjects

Research Procedures	Number of Samples/Procedures	Responsible Party	
		Study	3rd Party Payer or Participant
tDCS	1-10	x	
Neuropsychological Testing	3	x	
Telephone Interviews	2	x	
EEG testing	2	x	
MRI	2		
_____	_____		
_____	_____		
_____	_____		
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 tDCS employs extremely low currents and numerous studies have documented minimal risk of adverse events, any

adverse events requiring medical care will be extremely unlikely. Participants will not be charged for any of the experimental study procedures, including MRI scans. 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.

21. Compensation

Each of the 80 participants will receive$20/hr in the form of cash cards for taking part in the study. This is felt to be a fair amount that is not coercive and will help decrease attrition for this study which involves many visits.

22.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).

23.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.

Human participants who have suffered mmTBI (ages 18-55) will be recruited from the UNM Hospital ED and from other local Emergency Departments via phone call. If a patient shows interest in participating in our study, a brief prescreening will be done prior to initiating informed consent procedures. The prescreening procedures will assure that each potential participant meets study inclusion and exclusion criteria.
In regards to screening for pregnancy, female subjects will be asked if they are pregnant, not pregnant, or not sure. If a subject answers she is pregnant, she will be excluded from the study. If she answers not pregnant, she will be enrolled and advised to use two forms of birth control during the time of the stimulation phase of the study. If she answers that she is unsure, she will be offered a screening urine pregnancy test. If she is not able or willing to take the pregnancy test, she will be excluded from the study.

If, after prescreening, the 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 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.

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. Given the safety of tDCS to dorsolateral prefrontal cortex has been shown in numerous large controlled studies, it is highly unlikely that there to be any deterioration in decisional capacity as a result of the tDCS itself.

24. Documentation of Consent (see attached forms)

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

26. Sharing Study Progress or Results with Subjects

As the neuropsychological and EEG 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. 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. If the participant does not need an email and/or does not have an email address and does not want an email account, the email info@mrn.org will be added as the study record email. This will notify the RO team when the participant's scan has been read, and that a letter will need to be mailed to the participant's address on file.

27. Inclusion of Vulnerable Populations

There will be no gender restrictions with regard to sample inclusion. It is expected that our sample will reflect national sample characteristics of TBI populations; approximately 59% male and 41% female (CDC 2006). It is expected that our unselected sample, drawn from the ED at a large state-funded hospital, will result in TBI-group gender rations reflecting those of the CDC epidemiological sample. The age range of 18-55 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 55 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.

28. Community-Based Participatory Research NA

29. Research Involving American Indian/Native Populations NA

30. Transnational Research NA

31. Drugs or Devices

A NeuroConn (www.neuroconn.de) tDCS machine will be used to administer tDCS current. Square-shaped, 11 cm2 saline water (15mM) solution-soaked sponge electrodes, held by a rubber casing, are applied to the scalp using elastic bandage material. The anode will be placed on the scalp over the F3 target location and the cathode placed on the right upper arm below the deltoid. Current for the treatment condition will be applied at 2.0 mA for a total delivered charge of 60 mA-min.

Dr. Quinn as well as the research coordinator and technician who will be applying tDCS will undergo training with Dr. Vincent Clark, who is a national expert in tDCS and has published extensively on the safe and efficacious use of tDCS for cognitive enhancement. Dr. Quinn will also undergo training with his external mentor Dr. Marom Bikson, who is also a national expert on tDCS safety and mechanisms of action.

We have extensive experience using 11 cm2 sponges with 2.0 mA for 30 minute sessions, with excellent tolerability of skin sensation, and effective blinding of stimulation.[23] The use of 35 cm2 sponges spreads stimulation over a significantly larger area and reduces efficacy to achieve cortical excitability.[80,81] Given that our patient population is an outpatient, ambulatory, mild to moderate TBI population and that these current strengths and amounts have already been administered safely to patients with stroke and TBI lesions ipsilateral and proximal to the site of stimulation, we feel these parameters are extremely safe. Our group is currently studying tDCS in subjects with tobacco use disorder, alcohol use disorder, and schizophrenia and are finding the stimulation to be very safe and well tolerated. To date, 138 subjects have undergone published tDCS protocols with our group and only two subjects withdrew because of intolerable sensations. We find that about 1% of subjects on the average can't tolerate the skin stimulation caused by tDCS (heat, itching or burning sensations) and so we stop for them. The other 99% tolerate it well. We had one case of a system with a small piece of bare wire that touched the skin and caused a skin burn, which was small but needed attention. This can be avoided by having a tDCS setup with fully insulated wiring.

A Data Safety and Monitoring Board will review study data with the PI quarterly for any side effects or adverse events. The device will be kept behind locked doors at all times at the Clinical Core of the Center when not being used expressly for the current study. The principal investigator and trained research personnel will be the only persons with access to the device.

There are no long term neuropsychiatric effects from tDCS. With repeated stimulation, some subjects get dry skin. Applying lotion helps to ameliorate this. Using EEG gel rather than saline for the electrode conductor helps reduce this occurrence as well.

The 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 a use in supporting or sustaining human life
4) It is not for a use 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 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. The commonly reported side effects of TDCS are itching, burning, tingling, headache, and discomfort (10-40%), all of which are mild and transient. As this trial will be operating within standard parameters as defined

above, we believe our use of TDCS in subjects with mild-moderate traumatic brain injury represent a Non-Significant Risk.

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):

   Medical records

2. Describe the purpose for the review (e.g., screening):

   Screening

3. Describe who will conducting the reviews (e.g., investigators, research staff):

   Research staff

4. Do all persons who will be conducting the reviews already have permitted access to the data source?

   x☐ Yes

   ☐ No. Explain:

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

   a) The activity involves no more than minimal risk to the subjects 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.

      x☐ True

      ☐ Other justification:

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

      x☐ 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.

x☐ 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.)*

x☐ 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:

   x☐ 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.

   x☐ 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.

   x☐ 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 and 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.

<u>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.</u>

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

   .

2. Describe how capacity to consent will be evaluated.

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.

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

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

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

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.

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.

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: **Transcranial Direct Current Stimulator**

B. Manufacturer: **NeuroConn**

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*

x☐ No

D. Is the research IDE-exempt?

x☐ 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?

x☐ 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

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