Combined tDCS and cognitive training to improve attention and working memory in Active Duty Service Members with mild traumatic brain injury (mTBI)

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ABSTRACT

Objectives
The proposed study will evaluate a new approach to cognitive rehabilitation of mild traumatic brain injury (mTBI) using a brain stimulation technique called transcranial direct current stimulation (tDCS). Specifically, we will investigate how tDCS combined with cognitive training improves deficits to attention and working memory in Active Duty Service Members with a history of mild traumatic brain injury (TBI). Measures of attention-related brain activity, neurocognitive assessments, and self-reported clinical outcomes will be used to determine effects of tDCS vs. sham tDCS when paired with a cognitive training intervention. By doing this study, we hope to find a reliable, noninvasive, and efficient method of treating mild TBI cognitive symptoms.

Research Plan and Methods
This is a double-blind, randomized, placebo (sham) controlled pilot study. We will recruit 60 Active Duty Service Members who are receiving outpatient services at Naval Medical Center San Diego, with a history of mTBI and reported neurocognitive symptoms related to attention, working memory, and related cognitive processes. Intake will involve a full pre-assessment of symptoms, neurocognitive performance, and an optional MRI scan. Participants will be randomized to either active or sham tDCS. Training/tDCS sessions will occur daily over five consecutive days. Random permuted blocks will be used to ensure exactly equal treatment numbers at certain equally spaced points in the sequence of patient assignment. Post-intervention assessment will include another assessment of symptoms, neurocognitive performance, and an optional MRI scan. Participants will complete assessments of symptoms and neurocognitive performance six-weeks following the post-intervention assessment.

Clinical Relevance to DVBIC/Navy Medicine
Aspects of this study will provide insight into a major research gap highlighted in the mission of the Defense and Veterans Brain Injury Center, specifically in identifying/developing innovative treatments/interventions which promote patient recovery and/or mitigate symptoms after TBI. Novel, well-tolerated, neuroplasticity-based interventions that can improve attention, concentration, and working memory by targeting the underlying neural dysfunction are needed to improve outcomes and quality of life for Active Duty Service Members affected by neurocognitive weakness and dysfunction following mTBI. If tDCS proves successful in reducing TBI-related symptoms, improving cognition, or enhancing functional recovery, this non-invasive intervention could be implemented within various DoD and VA settings, enhancing recovery, improving quality of life, and bolstering occupational performance.
BACKGROUND

1.1 Traumatic brain injury (TBI) and cognitive dysfunction. Since 2000, there have been over 413,000 diagnosed brain injuries within the DoD. A large majority (82.3%) are classified as mild traumatic brain injury (mTBI), defined as structural injury or physiological disruption of the brain as a result of an external force, with loss of consciousness up to 30 minutes, post-traumatic amnesia up to 24 hours, alteration of consciousness up to 24 hours, significant neurological deficits, or intracranial lesion following the injury, though this number is believed to be underestimated given that mTBI often goes untreated and unreported. Nevertheless, individuals who sustain mTBI commonly report symptoms of difficulty with attention/concentration and memory problems, and a substantial minority continue to experience symptoms for more than three months, requiring more intensive intervention. Individuals who undergo traditional neuropsychological evaluation typically have profiles that are within normal limits (when they are valid) but may actually have a decline from premorbid functioning that cannot be evaluated without a prior baseline assessment. When objective support for a decline exists, it often reveals significantly impaired performance on measures of attention, concentration, and working memory—domains mediated by the dorsolateral prefrontal cortex (DLPFC).

1.2 Neurocircuitry dysfunction in attention and working memory systems. While the majority of neuropsychological studies in mTBI patients show intact neurocognitive performance, deficits reported by Active Duty Service Members and Veterans seeking care in TBI treatment programs are thought to be associated with diffuse microstructural axonal injury. Such injuries directly affect neural networks, like those involving the prefrontal cortex, compromising modulating functions critical to cognitive control. These include inhibitory control, attention, working memory, planning, risk taking, and delay discounting. The neural dysfunction caused by structural damage is evident in electrocortical activity recorded using EEG (electroencephalography) in mTBI patients during cognitive task performance and at rest. Notably, theta (4-8Hz), alpha (8-14Hz), and beta (25-35Hz) activity is frequently reported to be abnormal, wherein neural synchronization is dysregulated and functional connectivity is reduced in these frequency bands during executive function tasks. Studies observing individuals with TBI show poor intrahemispheric coherence in fronto-parietal and fronto-temporal and temporo-parietal regions, indicating impaired functional connectivity during a working memory task in these areas compared to controls. Dysfunctional neural activity secondary to mTBI is also evident in event-related potentials (ERPs) recorded during attention and executive function task performance. Deficits in early attentional processing are often revealed by reductions in amplitudes or delayed latencies of N1 and P1 components; similarly, reduced amplitudes and prolonged latencies of N2 and P300 observed in this population reflect impairments in cognitive control, including behavioral inhibition, working memory maintenance and context updating, and resource allocation. These patterns of task-specific neural dysfunction often correspond to impaired executive function.

Specifically, the dorsolateral prefrontal cortex (DLPFC) is implicated as a prime target for working memory and attention, with experimental work showing that modulation of this area yields improvement in executive function. Lateralization of the DLPFC is critical to optimizing cognitive control, as left DLPFC activation is associated with working memory and preparatory attentional adjustments and right DLPFC activation is associated with conflict resolution. Working memory and attentional control in patients with lesions to the left DLPFC and clinical patients (e.g., depression, TBI, multiple sclerosis) corresponds with hypoactivity in the left DLPFC and/or hyperactivity in the right DLPFC. This hemispheric imbalance of activity in the DLPFC is often associated with impaired cognitive control.
1.3 Interventions to enhance attention and working memory following mTBI. Rehabilitative efforts to improve cognitive function after mTBI vary by type and quantity, resulting in a dearth of well-controlled investigations that yield mixed results in terms of attention, working memory, and post-concussive symptoms. Though psychoeducational interventions have greater empirical support, they are considered less effective in their implementation among treatment-seeking Service Members with chronic TBI. As such, there is increasing support for compensatory interventions focused on attention and working memory, such as cognitive training and rehabilitation, within Active Duty Service Members and Veterans following mTBI.

1.3.1 Cognitive training to enhance attention and working memory. Cognitive training is an intervention designed to improve cognition through repetitive practice with the goal of improving cognitive performance on tasks such as attention, working memory, and problem solving. Preliminary studies using 10-week cognitive training programs showed improvements in prospective memory function, attention, and performance speed; fewer cognitive complaints; and greater functioning in Service Members with mTBI. Initial studies in Service Members with mTBI suggest that cognitive training can alter brain regions, neural circuitry, and behaviors. A meta-analysis of patients with ADHD and those at risk for working memory impairment (e.g. brain injured) showed that working memory training improved levels of inattention in daily life and those improvements persisted after training and remained significant at two to eight months post-training. Other studies of working memory training in populations such as learning difficulties, mood disorders, and anxiety showed improvements on clinical measures of impulsivity post-intervention. Finally, although results are mixed, several studies investigating cognitive training in disordered eating behavior have revealed improvements in cognitive flexibility pre- to post-treatment. Generally, cognitive training is shown to be effective for improving some cognitive abilities, though the process can be time and resource intensive, may be influenced by individual difference factors such as motivation, and may show a lack of generalization.

1.4 Transcranial Direct Current Stimulation (tDCS). To identify neural mechanisms for rehabilitation, research has incorporated non-invasive brain stimulation techniques that modulate neuronal firing and enhance cognitive training. tDCS applies a constant, low-amplitude direct current directed at the cortex using two surface electrodes (anode and cathode) applied atop the scalp. Anodal stimulation (cortical excitability via depolarization of the resting membrane potential) is applied on a given brain region, with standard parameters for stimulation between 5-30 minutes and intensity of current usually 1-2 mA (with a maximum of 4mA). The procedure is believed to increase regional activity, with immediate effects lasting a few hours and long-term effects lasting up to weeks to months after stimulation, depending on the frequency of sessions. Tasks can be performed either during stimulation (i.e., online tasks) or immediately following stimulation (i.e., offline tasks) to enhance the procedure. Because tDCS lowers the threshold for activation, but does not directly cause neurons to fire, the risk of harm from the procedure is minimal; most commonly reported side effects are mild tingling (70.6%), fatigue (35.3%) and slight itching at the onset of stimulation (30.4%). Other reported but infrequent symptoms include slight burning (21.6%) or mild pain (15.7%), though for all symptoms the intensity of these sensations were low.
Most common reported aftereffects are mild headache (11.8%), nausea (2.9%) or insomnia (.98%). Use of conventional tDCS safety guidelines have not produced any reports of serious adverse effects of injury following large review, and double-blind methodology has been successfully applied for intervention. Given its noninvasive means of implementation and ease of portability, it is a desirable method for modulating cortical excitability, enhancing neuronal firing, and encouraging long-term plasticity.

1.5 tDCS to improve attention and working memory in healthy populations. In populations of healthy participants, application of tDCS on the DLPFC has been shown to improve cognitive functioning, particularly working memory. Since the DLPFC provides the neural network for a wide array of cognitive functions affected by mTBI – most especially working memory – the use of tDCS in this area can show improvement across multiple neurophysiological mechanisms that impair neurocognitive performance. Though studies show existence of this effect, scholarly review across all tDCS studies to date show variation depending on stimulation parameters and tasks. For instance, a meta-analysis of 61 sham-controlled, within-subjects, single-session tDCS studies on the DLPFC in healthy individuals found faster reaction times, but not better accuracy for offline cognitive tasks. This was confirmed by another meta-analysis of 16 studies comparing healthy volunteers to neuropsychiatric patients in sham-controlled, single-blind studies. Singular studies have found that higher dose response (i.e., 2 mA over 1 mA) does not impact improvements among healthy participants, though meta-analyses suggest that higher current densities and longer stimulation durations do show greater enhancement of working memory. Thus, anodal tDCS on the DLPFC has consistently shown a general improvement in working memory in healthy populations, but the true potential of tDCS is unknown given the variety of methods and small sample sizes used in previous studies.

1.6 tDCS to improve attention and working memory in clinical populations. tDCS has been used in various clinical populations to improve attention and working memory function, including those with stroke, ADHD, Parkinson’s Disease, Alzheimer’s Disease, and a few limited initial studies in traumatic brain injury. Meta-analyses of neuropsychiatric patients (i.e., diagnosis of depression, Parkinson’s disease, or schizophrenia) who underwent anodal tDCS show small but significant improvements in working memory accuracy for performance tasks performed during tDCS. Parkinson’s patients who underwent tDCS with online cognitive tasks showed improvements in working memory immediately after their session and also greater executive functioning at 1-month follow-up after 10 consecutive sessions of tDCS with offline cognitive tasks. In contrast to healthy populations, there is some evidence that dose response and session time may have a greater influence on clinical populations than healthy populations. Boggio et al. found better accuracy on working memory tasks when Parkinson’s patients were given tDCS on the DLPFC at 2 mA, compared to 1 mA and sham conditions. Hoy et al. also found similar performance improvement for 18 schizophrenic patients on a working memory task following a single session of anodal tDCS applied to left DLPFC at 2 mA, compared to 1 mA and sham conditions. Cachoeira et al. used a 5-day course of treatment with anodal tDCS over right DLPFC (one 20 min session per day without a concurrent task) in adults with ADHD. They reported improvement in both attention and in functional outcomes (on a self-report measure of work, school and family life). These effects on attention and working memory may also generalize to other health outcomes.

The majority of studies showing a beneficial effect of tDCS on working memory have used anodal stimulation over left DLPFC. For example, of the 16 studies included in a recent meta-analysis by Hill et al. (2015) on the effects of anodal tDCS on working memory, all were left anodal (at electrode site F3), with the cathode placed over contralateral frontal areas (commonly over right supraorbital areas, or at site F4). These placements are consistent with observed lateralizations within the DLPFC suggesting that the left DLPFC, in particular, supports
working memory related processes. Right DLPFC, on the other hand, while not a passive area during working memory, supports cognitive processes that extend beyond the scope of working memory, such as those related to goal-directed behavior and adaptive decision making. Evidence suggests that right DLPFC plays a particular role in inhibitory control. Consistent with this role in inhibition, neuromodulation studies have shown that disruption of right DLPFC activity, e.g. with cathodal tDCS or low frequency repetitive TMS, can reduce its inhibitory activity and enhance memory performance. Much less work has been done investigating the effects on working memory of inhibiting right DLPFC activity than on enhancing that of left DLPFC; however, the extant evidence suggests that left anodal and right cathodal tDCS, in combination, is a promising approach for improving working memory.

1.7 Preliminary data on tDCS to improve attention and working memory in TBI. A few studies have applied tDCS to participants with mTBI, showing promising results. An initial pilot by Kang et al. (2012) recruited nine patients with mTBI to undergo a single, 20-minute session of anodal tDCS at 2 mA. Though not significant, mTBI patients showed reduced reaction time to a contrast reaction time task measuring attention, versus no change in the sham group. Finally, in a recent double-blind, placebo controlled clinical study of TBI patients (n = 26; n = 13 active, n = 13 sham) conducted by Ulam et al., tDCS was applied over the left DLPFC in patients with TBI for 10 consecutive days, with current intensity at 1mA. Greater improvement in working memory and attention was associated with increased power in the alpha frequency band and decreased power in the delta and theta frequency bands located around the anodal electrode, reflecting cortical excitability following tDCS in individuals with TBI. This provides evidence that EEG could detect excitability within the DLPFC caused by anodal tDCS. Moreover, these EEG changes were also associated with improved neurocognitive performance. Taken together, these results suggest that tDCS on the DLPFC may demonstrate significant improvements in working memory and attention within an mTBI population.

1.8 Task-dependent nature of tDCS-enhanced neuronal plasticity. Though researchers find promise in the use of tDCS on cognitively impaired populations, the reliable effect of tDCS alone is reportedly small given other available treatments and interventions. A growing consensus suggests that tDCS acts as a modulator of ongoing synaptic activity to facilitate task-relevant plasticity. This “functional specificity” has been illustrated in studies showing that tDCS preferentially facilitates long-term potentiation in a given neural network that is already activated (e.g. by a task or experimental stimulation), while not modulating separate neural networks that are inactive. tDCS can also enhance plasticity of circuits activated by task performance. A study directly assessing the relative effect of tDCS with cognitive training (n-back task) found reliably greater improvement in performance on a digit span forward span task compared to sham and tDCS alone. These findings underscore the potential value of cognitive activity concurrent with stimulation to enhance the efficacy and specificity of tDCS.

1.9 tDCS-enhanced cognitive training. This preferential enhancement of plasticity in activated neural networks supports investigation of paired tDCS and cognitive training to modulate learning and cognitive functioning. A major limitation of tDCS-only enhancement of working memory is that it leads to increased speed without increased accuracy on working memory tasks. Given this limitation, protocols interested in broader cognitive effects in healthy populations are increasingly using concurrent tDCS stimulation with cognitive training. Within clinical contexts, tDCS has been applied to enhance the efficacy of rehabilitation or cognitive training with increased enhancement of performance outcomes. Researchers point to evidence of substantive tDCS-enhanced effects once cognitive training begins, and better generalization with right DLPFC stimulation. However, similar to single session tDCS-enhanced training, the broad generalization of training with multiple sessions has shown limited results from cases with few online or no tasks during stimulation. Thus, we
hypothesize that generalization requires more comprehensive sets of training tasks focused on attention and working memory, and a larger “dose” of tDCS-enhanced cognitive training.

1.10 Preliminary studies
Relevant to this proposal, we discuss several studies by our investigators and collaborators that examine the use of cognitive training in clinical populations. Studies from colleagues at VA Minneapolis demonstrate how cognitive training affects brain activity using fMRI, how tDCS can be used to increase the generalization of cognitive training, and how tDCS, when combined with cognitive training, results in specific neural circuitry changes. In addition, findings from an associate investigator-led study demonstrate additional effects of cognitive training, specifically in a TBI population.

1.10a Evidence that shorter cognitive training can also modulate fMRI-measured resting state functional connectivity following mTBI.
As part of the NeuroDRIVE clinical trial, researchers from our group examined 24 participants with history of either a mild, moderate or severe TBI. Of those, 11 underwent a 4-week, 6-session virtual reality intervention that emphasized cognitive skills such as dual processing, working memory, and response inhibition through standardized driving scenarios. Participants completed an n-back task and a resting state scan pre- and post-intervention. Examining activation in Visit 1 specific to working memory (1-back minus 0-back) showed increased activity in bilateral DLPFC and prefrontal cortex, anterior insula, medial superior frontal gyrus, left thalamus, bilateral supramarginal / angular gyrus, precuneus, and left posterior middle temporal gyrus. Patients who received cognitive intervention showed reduced activity related to working memory load for the group that went through the intervention compared to the control group, demonstrating increased efficiency with increasing task difficulty. This study provides preliminary evidence that cognitive rehabilitation for working memory and visual attention was associated with enhanced functional activation in a sample of individuals with TBI.

1.10b Evidence that cognitive training can modulate fMRI-measured prefrontal neuronal activation.
Our colleagues at the VA Minneapolis compared functional magnetic resonance imaging (fMRI) measured brain changes among 9 schizophrenic patients who received cognitive remediation training for 4-6 weeks, 9 schizophrenic patients who received cognitive behavioral social skills training for 4-6 weeks, and 9 healthy controls (no training). Participants were scanned 6-8 weeks apart with training between scans. Schizophrenic patients receiving cognitive remediation training increased activation in a network that included dorsolateral/frontopolar cortex and anterior cingulate when compared with both patient controls and healthy controls. The extent of activity increase was predicted by their cognitive performance. This was the first study to demonstrate that cognitive training was associated with increases in dorsolateral prefrontal activation as measured by fMRI.

1.10c tDCS augmentation of executive function training enhances near and far transfer. In a single-blind, sham-controlled, randomized, proof of concept study, cognitive training (practicing a working memory task) was provided in 3 weekly sessions for 16 weeks to participants with schizophrenia. Beginning in week 3 of training, tDCS or sham stimulation was applied concurrent with the first 20 min of training during two sessions each week (total 28 sessions). 1mA was administered over F3 (anodal) and the contralateral supraorbital position (FP2; cathodal). Magnitude of intervention-induced change was measured using The MATRICS Consensus Cognitive Battery (MCCB), a standardized measure of cognition in patients with schizophrenia, and compared between participants who received cognitive training only (sham-tDCS; n=4) and participants who received cognitive training plus tDCS (n=6). Near transfer effects were revealed, demonstrating greater improvement in Word 2-back tasks (F(1,6)=9.13, p=0.01, partial η2=.60), and picture n-back tasks (F(1,6)=6.94, p=0.04, partial η2=.54) for tDCS.
Preliminary evidence of far transfer effects were found via improvement in the untrained MCCB for active tDCS (post-pre $d = .48$) compared to sham groups (post-pre $d = .34$; group x time $F[1,6]$, ns, partial $\eta^2=.08$). This preliminary study shows that tDCS concurrent with cognitive training is feasible and well tolerated in a clinical population and increases near and far transfer of cognitive training.

1.10d Active tDCS and concurrent cognitive training increases striatal-frontal functional connectivity. In a pilot randomized controlled study of participants with alcohol use disorder (AUD), our colleagues at VA Minneapolis have collected baseline and follow-up resting state fMRI scans for 11 AUD participants. Six subjects who received active tDCS (2 mA anode over left DLPFC, cathode over right DLPFC) were compared to five subjects who received sham tDCS. Intervention sessions were 46 minutes (13 min tDCS - 20 min off - 13 min tDCS), for five consecutive days; all participants underwent concurrent cognitive training (the Reversal Learning task and BART) during the 46-minute session. Resting state fMRI data was collected pre- and post-intervention. Analyses examining prefrontal (dorsolateral)-NAcc resting state functional connectivity (RSFC) revealed a significant Group (active tDCS vs sham tDCS) x Time interaction in RSFC ($F=7.105, p=0.026$; eta-square $\eta^2=0.441$; Figure 3). Only those assigned to active tDCS showed prefrontal-NAcc RSFC increase across time. Further, four-month follow-up data found that those who received active tDCS + cognitive training had a significantly longer time to relapse than those with sham tDCS + cognitive training ($M_{diff} = 91$ days, $p=0.021$). These pilot data suggest that tDCS combined with cognitive training can increase frontal-striatal functional connectivity. In the current proposal, mTBI participants will undergo similar cognitive training + tDCS paradigm with predicted improvements in relevant outcomes.

**PURPOSE**

Difficulty with attention, concentration, and working memory are the most reported neurocognitive sequelae following mild traumatic brain injury. These difficulties are present in many brain disorders commonly seen in Active Duty Service Members, including traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), and substance use disorders. Unfortunately, there are very few effective treatments that target attention and working memory directly. Novel, well-tolerated, neuroplasticity-based interventions that can improve attention, concentration, and working memory by targeting the underlying neural dysfunction, are needed to improve outcomes and quality of life.

![Figure 2. Larger intervention effect when combining cognitive training (CogTrain) plus active tDCS. Light blue bars show degree of intervention-induced change in schizophrenia patients that underwent CogTrain+active tDCS. Dark blue bars show degree of intervention-induced change in schizophrenia patients that underwent sham tDCS.](image1)

![Figure 3. Change in resting state functional connectivity (RSFC) between prefrontal cortex and nucleus accumbens (Nacc). Participants receiving active tDCS+cognitive training (red bar) showed significantly greater RSFC change than those receiving sham tDCS+cognitive training.](image2)
of life for Active Duty Service Members affected by neurocognitive weakness and dysfunction following an mTBI.

To date, the combined effects of cognitive training and tDCS on attention and working memory have not been investigated in Active Duty Service Members. Colleagues from the Minneapolis VA have demonstrated effective and durable results targeting impulsivity,\(^8^3\) a deficit modulated by the same gross brain regions as attention and working memory—namely the dorsolateral prefrontal cortex. The reliable use of tDCS to enhance frontal-striatal connectivity and long-term plasticity in humans, coupled with pilot data demonstrating the efficacy of active tDCS and concurrent cognitive training in patients to improve health outcomes, show promise with respect to rehabilitating attention and working memory in Active Duty Service Members impaired from mild TBI.

**SPECIFIC AIMS**

The primary objective of this study is to investigate the effect of a novel neuroplasticity-based intervention for attention, concentration, and working memory that combines cognitive training and transcranial direct current stimulation (tDCS) to improve cognitive functioning, outcomes, and quality of life for Active Duty Service Members who have sustained mild traumatic brain injuries.

**Aim 1: Compare effects of active vs. sham tDCS paired with cognitive training on attention and working memory.** Active Duty Service Members with a history of remote mild traumatic brain injury and reported difficulty with neurocognitive functioning will be randomized to receive either active tDCS or sham tDCS in conjunction with training tasks targeting attention, concentration, and working memory.

H1: Active compared to sham tDCS will produce significant improvements in both self-reported and objective measures of attention and working memory.

H2: Active compared to sham tDCS will produce significant improvement in functional and quality of life outcome measures.

**Aim 2: Compare effects on brain activity changes between active vs. sham tDCS paired with attention and working memory tasks.** Brain activity changes will be measured by electroencephalography (EEG) and fMRI data (when available) collected pre- and post-intervention. Using the EEG modality, brain activity (e.g. event-related potentials (ERPs), spectral power, frontal asymmetry, functional connectivity) will be measured during rest and while performing tasks (e.g., Fusion n-back task) requiring attention and working memory. Using the fMRI modality, functional connectivity during resting state, blood flow in the brain, and structural integrity of white matter will be examined.

H3: Active compared to sham tDCS will produce significant improvement in attention-related brain measures (e.g. decreased delta and theta power, increased alpha power, and increased functional connectivity).\(^6^5\)

Exploratory H4: Determine whether brain activity changes are related to changes in outcome neurocognitive measures.

Exploratory H5: Active compared to sham tDCS will produce a significant change in attention and working memory related brain regions and their functional connectivity with other regions of the brain.
METHOD

Study Design
This study will be a double-blind, randomized, placebo (sham) controlled study. A pilot sample of 60 participants will be recruited from the NMCSD TBI clinic and Emergency Department and randomly assigned to receive either active or sham tDCS, both paired with cognitive training tasks. Intake will involve a full pre-assessment of symptoms, neurocognitive performance, and an optional MRI scan. Training/tDCS sessions will occur daily over five consecutive days. Post-assessment will occur at 4 days and six-weeks following the five-day sessions.

RECRUITMENT
This study will recruit 60 Service Members who are receiving either outpatient services or emergency room care at Naval Medical Center San Diego. Participants will be recruited by clinical staff, from publicizing materials (e.g., posted flyers), and patient lists from clinics within NMCSD based on the participant’s clinical history of traumatic brain injury. Some methods of recruitment will include:

- Publicizing materials (such as flyers) will be posted in applicable NMCSD clinics and venues with permission from the departments. Clinicians located in these clinics will be provided with flyers and study cards to give to interested patients.
- We will publicize the study through various forms of media. Future possibilities include but are not limited to Military Base newspapers and magazines. Additionally, we may post a brief advertisement on Military social media sites (e.g. Facebook, Twitter feeds).
- With permission from event organizer(s) and/or if invited, we will attend and/or contribute to related meeting and events outside of NMCSD. Some methods may include, but are not limited to, giving a short presentation on participation opportunities, providing flyers, study cards, or attending the meeting and collecting contact information from interested potential participants.
- Respective San Diego military venues will introduce the research opportunity to Service Members and, if interested in learning more about the study, will offer the contact details of the tDCS study research team, and/or offer to pass on their contact details to the research team who will contact them directly.

The NMCSD TBI Clinic provides a comprehensive program of care to approximately 40 Active Duty Service Members per month. Since January 2014, approximately 2000 Service Members have been consented into the TBI registry, allowing them to be contacted for participation in research. Recruitment from the VA Minneapolis pilot study yielded 30 participants per year with dropout rates at 10% and 16% at the 1 month and 2-month follow-up sessions, respectively. With a conservative estimate of 20% participant attrition and/or unusable data (e.g. poor signal quality) over the entire study period, our recruitment goal would yield approximately 48 completed participants in the final study cohort. Data from this study sample will be used to estimate effect sizes for follow-up larger scale research studies (see Section 4.12 Sample Size Calculation/Power Analysis). Recruitment will conform to HIPAA requirements for protection of private health information.

Identification and Selection of Subjects
A total of 60 male and female Active Duty Service Members who have incurred a mild TBI and seeking outpatient services will be recruited from the TBI clinic located at NMCSD. These individuals must be symptomatic for neurocognitive impairment related to attention, concentration, working memory, or memory (see Inclusion Criteria).

Individuals who have ever experienced any loss of consciousness, alteration of consciousness, or post-traumatic amnesia related to blunt force trauma or explosive blast will be considered to have a history of possible TBI.
The study investigator or research team member will approach/contact the patient, introduce the research opportunity and, if interested, the participant will be screened for study eligibility. Service Members who are enrolled in the study based on a self-reported history of traumatic brain injury can then be verified via medical record review in AHLTA prior to pre-screening.

**Inclusion Criteria**
Participants will be included in this study if they:

1. Have a remote history mild traumatic brain injury as defined by the VA/DoD clinical practice guidelines that is $\geq 6$ months, and report moderate severity neurocognitive symptoms related to attention, concentration, working memory, or memory based on NSI scores and self-report.
2. Are between the ages of 18-55.
3. Are stable on any medications for at least 2 weeks at the baseline visit (Visit #1).

**Exclusion Criteria**
Participants will be excluded from this study if they:

1. Have a history of seizures or epilepsy.
2. Have a history of ECT or cortical energy exposure within the past 12 months, including participation in any other neuromodulation studies.
3. Have current stimulant dependence.
4. Have a diagnosis of intellectual disability or pervasive developmental disorder (i.e. premorbid IQ less than or equal to 70).
5. Have any medical condition or treatment other than mild TBI (e.g. stroke, tumor, HIV, moderate-severe TBI), with significant neurological disorder or insults that, based on the Principal Investigator’s judgement, would impact risk.
6. Diagnosed with current active psychosis or mania.
7. Have metallic cranial plates/screws or implanted device,
8. Have eczema on scalp or other scalp lesions or skin disorders that may become irritated by stimulation.
9. Pregnant individuals and individuals with ferromagnetic metal in their body that would prohibit them from being safe in the MRI will not be excluded from the overall study, but will be excluded from the optional MRI.

**Pre-screening**
Potential participants will be contacted by a member of the research team (see Phone Script document). The service member will be provided an overview of the research and will have the opportunity to ask questions.

He/she will be asked to give a verbal consent in order to start the screening process. IRB-approved waiver of Informed Consent and waiver of HIPAA Authorization allow verbal disclosure of health information to determine study eligibility during the study’s screening process (see **Exclusion Criteria**). The information disclosed will not be recorded on paper or via any other means.
During this pre-screening interview, information will be obtained regarding demographics, military status, medical history, and supplemental questions related to TBI history. This information will be used for the purpose of confirming study eligibility related to TBI and other inclusion/exclusion criteria.

Individuals who are determined to be eligible will then be offered optional MRI scans at the Baseline Session (Visit #1) and the Post-Intervention Session (Visit #7). Participants who agree to MRI scans will be screened for safety using the MRI screening questionnaire and scheduled accordingly for participation in the study. Those who decline to undergo MRI scans will be scheduled accordingly for participation in the study.

Randomization Process
Following enrollment in the study, participants will be randomized to either active or sham tDCS. Random permuted blocks will be used to ensure exactly equal treatment numbers at certain equally spaced points in the sequence of patient assignment using Random.org “Random Integer Set Generator”.

**Setting blocks:** Random.org – Random Integer Set Generator

**Step 1: The Sets.**
- Generate 5 sets with 4 unique random integers in each
- Each integer should have a value between 1 and 5

**Step 2: Display Options**
- Only “print the sets in the order they were generated” should be selected

**Step 3: Go!**

Record the integer set into the Participants timeline:
Task Order (Acronym Alphabetical):

1. CS = Card Shark
2. DD = Double Decision
3. LT = To-Do List Training
4. SS = Syllable Stacks
5. TT = Target Tracker

Informed Consent Process
If the individual is determined to be eligible for the study, the IRB approved informed consent will be obtained by study personnel at a later date. The consent form will be explained to each participant and their questions will be answered. The study personnel will ensure that each participant is fully informed about the objectives and potential risks of the project as it is reviewed and approved by the Naval Medical Center San Diego Institutional Review Board (IRB) prior to initiating studies. It will be noted to each participant that participation is voluntary and that they may withdraw from the study at any time.

Because this research involves military personnel, unit officers and noncommissioned officers (NCOs) shall not influence the decisions of their subordinates to participate or not participate as research subjects. Unit officers and senior NCOs in the chain of command shall not be present at the time of screening and consent.

Withdrawal from/Discontinuation of Participation
The participant has the right to withdraw from this study at any time and does not need to provide a reason from withdrawing from the study if they decide to do so. If the participant decides to stop taking part in this study, they should notify the Principal Investigator as soon as possible. Any data that has been collected up until that point will be used in data analysis. The Principal Investigator may withdraw the participant from the study if circumstances arise which warrant doing so.
Intervention Protocol
Cognitive training, using the 5 BrainHQ tasks (see below), will occur concurrently with tDCS, in both the active and sham tDCS groups during intervention sessions. Order of task presentation will be randomized each session (see Figure 4 for timeline of an intervention session).

Brain HQ
We hypothesize that using tasks (i) designed for cognitive training, (ii) that target the DLPFC more generally, (iii) that are engaging for the participant, and (iv) that adapt to their performance, should enhance the effects of tDCS on attention and working memory. BrainHQ (Posit Science) is a commercially-available suite of cognitive training tasks that are both engaging and adaptive based on participants’ performance. More than 60 peer-reviewed medical and science journal articles have been published on the benefits of BrainHQ exercises and assessments in varied clinical populations. Its commercial availability also makes BrainHQ amenable to potential future large-scale deployment. Training occurs on a computer and consists of four exercises selected to (i) place demands on attention and working memory, (ii) adapt to challenge the participant’s current ability level, (iii) provide ongoing feedback, and (iv) present novel stimuli across visual and auditory modalities for broader spatial activation. Five training tasks are drawn from the commercially-available BrainHQ suite of tasks based on their relevance to visual attention and working memory, and empirical evidence of training gains given the study parameters (see Table 2). Over each 46-minute daily training period, 4 of 5 tasks will be performed for approximately 11 minutes in a randomly selected order (see Figure 4 for timeline of an intervention session). Following the completion of each training period, participants will be asked to supply a subjective workload assessment. Participants may answer questions regarding their level of effort, mental demand, frustration, physical demand, temporal demand, and performance on the 4 tasks completed during the training period. For example, questions such as “How mentally demanding was the task?” or “How much effort did it take to complete this task?” may be asked.

Table 2: BrainHQ Attention and Working Memory Tasks.

<table>
<thead>
<tr>
<th>Task</th>
<th>Modality</th>
<th>Domain</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double Decision</td>
<td>Visual</td>
<td>Attention</td>
<td>Expand your useful field of view and speed up brain processing for faster reaction time and safer navigation.</td>
</tr>
<tr>
<td>Target Tracker</td>
<td>Visual</td>
<td>Attention</td>
<td>Try to keep track of objects in motion as you flex your divided attention skills.</td>
</tr>
<tr>
<td>Card Shark</td>
<td>Visual</td>
<td>Intelligence/Decision-making</td>
<td>Remember the values of multiple cards and quickly compare them, challenging your brain to keep multiple pieces of visual information in mind at once and sift through them.</td>
</tr>
</tbody>
</table>
Syllable Stacks | Auditory | Memory | Work on your ability to remember spoken information in order.
--- | --- | --- | ---
To-Do List Training | Auditory | Memory | Work out your working memory, a form of short-term memory that's a critical part of almost all cognitive tasks related to thinking.

Accessing BrainHQ

BrainHQ subscription is necessary to play more than one game per day. BrainHQ research accounts are available for discounted purchase at $72/year. The number of accounts are determined by the number of participants run simultaneously for the study. Only one Gmail account is required to run participants. See BrainHQ research study details on how to set up a participant sessions.

Login: tdcstbistudy@gmail.com
Password: NMCSDtduc

Participants will have random permuted blocks for the assignment of their cognitive tasks:

**Example Participant T104:**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Session</th>
<th>Stimulation</th>
<th>tDCS</th>
<th>Cognitive Training</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>LT</td>
<td>CS</td>
<td>SS</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>SS</td>
<td>DD</td>
<td>TT, CS</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>CS</td>
<td>TT</td>
<td>SS, LT</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>DD</td>
<td>TT</td>
<td>SS, LT</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>CS</td>
<td>TT</td>
<td>LT, DD</td>
</tr>
</tbody>
</table>

CS = Card Shark; DD = Double Decision; LT= To-Do List Training; SS = Syllable Stacks; TT = Target Tracker

Record the **DAY, TIME, and ORDER** of all participants on their participant tracking sheet (See: Visits).

Setting up a participant’s individual session.
See BrainHQ Research Portal steps [here](#)

How/where to save participant performance.
See BrainHQ Research Portal steps [here](#)

tDCS/Neuroelectrics System

We will use the **Neuroelectrics Starstim 8 system**, a wireless multichannel transcranial current stimulator. Similar to previous research, conventional tDCS (1 anode and 1 cathode) will be used for this study in order to provide the greatest enhancement of cortical plasticity while activating combined with cognitive functions known to be impaired following mTBI.⁸⁴,⁸₅
**NIC2 Software**: The Neuroelectrics® Instrument Controller (NIC2) is an integrated environment for end-to-end management of Starstim® and Enobio® devices from your computer. This powerful platform offers basic and advanced modes to design and monitor any experiment involving electroencephalography (EEG) and/or transcranial electrical stimulation (tES). Moreover, it provides handy access to all relevant instructions for use of our systems and methods to integrate Neuroelectrics® devices in real-time with other systems. NIC2 is a part of all Neuroelectrics® systems.

**Neoprene Headcap**: The Neoprene Headcap is a comfortable, reliable and flexible solution to place electrodes for EEG monitoring and tES stimulation. Its positioning grid with 39 predefined and clearly annotated positions is based on a subset of the international 10-10 EEG system. Extra positions can be created using the neoprene punchtool. The cap is available in four adult-sized models (XL, L, M, S). Two extra kid-sized models (K, KS) can be acquired with the Kid Neoprene Cap.

**Sponstim**: The Sponstims are a family of sponge-based electrodes suitable for any type of transcranial electrical stimulation with Starstim® and Starstim®-Home, including tDCS, tACS and tRNS waveforms. The Sponstim electrodes offer a range of different shapes and sizes to suit various experiment requirements. The circular model with 25 cm² and the rectangular model with 35 cm² provide a large, comfortable and reliable contact, which is ideal for bipolar (anodal or cathodal) experiments. The smaller Sponstim models, one with a circular area of 8 cm² and one with pellet area of π cm², are the solutions designed for multi-electrode tES. All models must be used with saline solution.

**Active tDCS**

Based on previous studies targeting working memory, focality of current delivery, and comfort and tolerance levels, we will use a 2 mA current administered via two circular carbon rubber core electrodes in saline-soaked surface sponges (25 cm²), placed in a neoprene headcap with marked locations based on the 10-10 EEG system. The anodal stimulating electrode will be at location F3, over left dorsolateral prefrontal cortex (DLPFC) and cathodal electrode at location F4, over right DLPFC. Two reference electrodes, CMS and DRL, will be attached to the EarClip and applied to the earlobe with conductive gel. CMS/DRL contact is necessary to perform impedance checks during stimulation.

The Starstim software supports the measurement of electrode impedance. Before each training session, the impedance of the electrodes will be checked and verified to be ≤15 KOhm. During a training session, the impedance is measured

![Figure 5. Computational modeling showing the magnitude of the electric field induced during bihemispheric tDCS over the DLPFC (front view of the brain). Peak volt/meter values are predicted in cortical gyri consistent with the prefrontal subregions of interest. Modeled using the NIC 2.0 Software Suite (StarStim)](image-url)
every second and if found to be > 20 KOhm stimulation will be terminated for safety. The current and impedance will be recorded for every session.

Figure 5 illustrates the effectiveness of this tDCS configuration for stimulating the left DLPFC. The figure was generated by our colleagues at the Minneapolis VA for another study using the same tDCS parameters.

Sham tDCS
For sham stimulation, the electrodes will be placed at the same positions as for active stimulation (F3 and F4). After an initial ramp-up period of 30 seconds, stimulation fades out over a period of 30 seconds. Additionally, at the end of the sham stimulation period, stimulation will fade in over a period of 30 seconds and then end with a final 30 second ramp-down period. Participants will feel the initial itching sensation associated with tDCS and experience the ramp-down period at the end of the sham stimulation period but will receive no active current during the rest of the sham stimulation period. This method of sham stimulation has been shown to be reliable. The Starstim software supports the measurement of electrode impedance. Before each training session, the impedance of the electrodes will be checked and verified to be ≤15 KOhm. During a training session, the impedance is measured every second and if found to be > 20 KOhm stimulation will be terminated for safety. The current and impedance will be recorded for every session.

Starstim System Setting Parameters
For detailed description and user instructions, refer to the Neuroelectrics Starstim 8 user manual at https://neuroelectrics.com:3001/downloads/NE_UM_P1_SS_2.7_EN.pdf.

Conditions of Use. Starstim must be used with normal temperature, humidity, and pressure conditions:
- Temperature Range: +5 to 40°C (41 - 104°F)
- Humidity: 15-93%
- Atmospheric Pressure: 700-1.000 hPA.

Conditions for Storage:
- Temperature Range: -25-65°C (-13 - 149°F)
- Humidity: 15-93%

Testing the System
The Starstim 8 system includes a testboard which allows stimulation protocols to be tested before performing them on a participant. The testboard is also a convenient tool to troubleshoot issues with the hardware. This tool can determine whether the root cause of high impedances issues is the device, cables, or configuration.

Setting the Double Blind Feature
The Starstim 8 system offers an end-to-end solution for fully reliable double blind studies through the NIC2 software. The whole system can be run in the special password-protected mode – minimizing the information presented on the screen for the definitive blinding of a researcher and study participant.

A member of the research staff who is not involved in the study will create and manage the protocols in NIC2. These protocols will be given generic names that do not reveal any information regarding the type of stimulation. This staff member will enter a password in NIC2 to activate the double-blind mode. This password will not be shared with any of the researchers conducting the experiment. When the double-blind mode is activated, non-essential information is hidden.
Setting the Sham Condition Parameters

For sham stimulation, the electrodes will be placed at the same positions as for active stimulation (F3 and F4). When the sham condition is activated, additional settings become available to set the duration of the fade-out and fade-in periods at the beginning and end of the sham stimulation period, respectively. The fade-out and fade-in durations will be set to 30 seconds each. These settings will create a sham stimulation where participants experience the same sensations as active tDCS stimulation at the beginning and end of the session, but receive no active current during the rest of the stimulation period.

Electroencephalogram (EEG) Acquisition and Data Extraction

EEG will be recorded during rest and performance of generalization tasks (e.g., Fusion Task) at pre-intervention baseline (Visit #1), post-intervention (Visit #7), and six-week follow-up (Visit #8).

EEG will be recorded using a Cognionics EEG array consisting of 25 electrodes conforming to the international 10-20 electrode placement system. In this system, participants wear a cap that contains electrodes that make contact with the scalp. In addition to the scalp electrodes, participants will be fitted with electrodes clipped to the ears to obtain measurements of electrical interference.

Raw EEG data are likely to be contaminated with noise artifacts. Several pre-processing steps are required to boost the signal-to-noise ratio. First, data contaminated by noise artifacts must be corrected or rejected using signal processing techniques. Independent component analysis will be performed to extract artifacts such as eye movements, eye blinks, and heartbeat components from the raw EEG data. EEG data will then be bandpass filtered to remove low and high frequency artifacts and re-referenced to the average of all electrodes.

Here we list the measures of neural dynamics that we plan to compute, although additional ones might be included and/or developed as we progress in the project:

**Spectral Power:** Following artifact detection and correction, data at each EEG electrode will be spectrally decomposed into the following frequency bands: delta (1-3 Hz); theta (4 to 8 Hz), alpha (8 to 12 Hz), beta (13 to 30 Hz), and gamma (30 to 40 Hz). The power at each frequency band will be quantified relative to total power (1-40Hz). A frontal asymmetry index will be computed for each frequency band as the difference between power measured at frontal channels over the left versus right hemisphere.

**Functional Connectivity:** Intrahemispheric functional connectivity (e.g. coherence, phase-locking) will be computed between fronto-parietal, fronto-temporal, and temporo-parietal regions. Interhemispheric functional connectivity will be computed over the frontal region.

**Mean ERP Amplitude:** Task-based EEG data will be segmented into epochs for each stimulus/event and averaged over trials to produce event-related potentials (ERPs). ERP components will be identified by visual inspection with regard to conventional measurement parameters for each component (e.g., P1 is typically maximal over occipital regions between 80-130ms after stimulus onset). Mean amplitudes of ERP components - both sensory level (e.g. P1, N1) and cognition-related (e.g. N2, P3) will be extracted from the ERPs.

Fusion

In the Fusion Test, participants will complete various tasks in which they will see stimuli (e.g. shapes, colors, etc.) appear on the screen. Participants will respond to the stimuli by pressing buttons on a response pad.
Simultaneously, saccadic RT targets (circles or other shapes) will appear on the screen. Participants will be instructed to momentarily shift their gaze to the saccadic targets once they appear. Concurrently, participants will press buttons to indicate the correct response to each target. Following the completion of sub-components of the task, participants will be asked to supply a subjective workload assessment. Participants may answer questions regarding their level of effort, mental demand, frustration, physical demand, temporal demand, and performance on each task. For example, such questions as “How mentally demanding was the task?” or “How much effort did it take to complete this task?” may be asked.

Magnetic Resonance Imaging (MRI) — Optional
Participants may undergo optional magnetic resonance imaging (MRI) of the brain on a 3T MRI system. The MRI scan sessions will last approximately 45 minutes. Subjects who undergo MRI scans will be screened for MRI safety using the screening questionnaire. Pregnant individuals and individuals with ferromagnetic metal in their body that would prohibit them from being safe in the MRI will not undergo MRI imaging. No contrast agents will be injected for the purpose of this study. Images obtained may include structural MRI, susceptibility weighted imaging (SWI), Diffusion tensor imaging (DTI), Pseudo-Continuous Arterial Spin Labeling (pcASL) and resting state functional MRI (rs-fMRI). If image quality of a given sequence is inadequate, due to patient motion for example, the sequence may be repeated at the discretion of the MRI technologist or radiologist. MRI data collected as part of this study are intended for research use only. However, any incidental findings will be reviewed by study investigators, with a referral for clinical follow up as indicated. All MRI data collected will be transferred to the research laboratory for analysis.
## VISITS

<table>
<thead>
<tr>
<th>Task Name</th>
<th>Task Type</th>
<th>Visits #1</th>
<th>Visits #2-6</th>
<th>Visits #7</th>
<th>6-week follow-up</th>
<th>Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent, HIPAA</td>
<td>Regulatory</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>20 min</td>
</tr>
<tr>
<td>OSU-TBI-ID</td>
<td>Structured interview to assess past head trauma (staff-administered)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>25 min</td>
</tr>
<tr>
<td>MRI Brain w/out Contrast (optional)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>45 min</td>
</tr>
<tr>
<td>Pre and Post tDCS Symptom Rating Questionnaire (SRQ)</td>
<td>Questionnaire to assess symptoms pre and post stimulation</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>5 min</td>
</tr>
<tr>
<td>NIH Toolbox Quality of Life assessment</td>
<td>Questionnaire to assess quality of life with regard to cognitive, social, emotional, and behavioral abilities (49 questions)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>20 min</td>
</tr>
<tr>
<td>Neurobehavioral Symptom Inventory</td>
<td>Measure of common post-concussive symptoms</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>5 min</td>
</tr>
<tr>
<td>Insomnia Severity Index</td>
<td>Measure of insomnia severity</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>5 min</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test</td>
<td>Measure of visual attention and working memory</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>10 min</td>
</tr>
<tr>
<td>NAB Attention Module</td>
<td>4 subtests to assess visual and auditory attention, working memory, and scanning.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>10 min</td>
</tr>
<tr>
<td>Fusion Task</td>
<td>Multi-modal assessment of brain function including EEG and eye tracking</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>20 min</td>
</tr>
<tr>
<td>tDCS/Sham</td>
<td>Intervention</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>50 min</td>
</tr>
</tbody>
</table>
EEG (set up and resting)  EEG will be collected to assess neural dynamics during rest and during performance of generalization tasks.

(30 min set up-done during questionnaires) + 6 minutes resting

Cognitive Training Protocol (BrainHQ Tasks)  Computerized cognitive training tasks (see Table 2 for details)

46 min (completed during tDCS)

Baseline Session (Visit 1)
At the baseline visit, participants will provide informed consent prior to beginning any of the study protocol. Prior to consent, participants will be screened with the same questions asked over the phone. If they are eligible, participants will be consented and complete the Baseline Interview and Contact Information. Next, participants will be assessed with OSU-TBI-ID, NIH QOL, NSI, ISI, SDMT, and NAB Attention Module. Participants will then be fitted to EEG and eye tracking equipment to assess neural dynamics during the Fusion task. Participants who undergo MRI scans will then be escorted to NMCSD Radiology to have an MRI scan performed. The visit length is expected to be approximately 190 minutes total.

Intervention Sessions (Visit 2-6)
During tDCS, patients will complete cognitive training computer tasks. Five training tasks will be drawn from BrainHQ based on their relevance to visual attention and working memory: Card Shark, Double Decision, To-Do List Training, Syllable Stacks, and Target Tracker. Each of 4 tasks will be performed for approximately 11 minutes in a randomly selected order. Random permuted blocks will be used to ensure exactly equal treatment numbers at certain equally-spaced points in the sequence of patient assignment.

Stimulation sequences will occur in the first 13 minutes (shut off: Minute 13) of the session and the last 13 minutes of the session (turn on: Minute 33). The Symptom Rating Questionnaire (SRQ) will be asked before and after stimulation to assess for any side-effects. The visit length is expected to be approximately 46 minutes each.

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>tDCS --------</th>
<th>Task 1</th>
<th>Task 2</th>
<th>Task 3</th>
<th>Task 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Training</td>
<td>Off (Min 13)</td>
<td>Min 0 – 11</td>
<td>Min 12-23</td>
<td>Min 24-35</td>
<td>Min 36-44</td>
</tr>
<tr>
<td>On (Min 33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Visit 2  Session 1
Visit 3  Session 2
Visit 4  Session 3
Visit 5  Session 4
Visit 6  Session 5

CS = Card Shark; DD = Double Decision; LT= To-Do List Training; SS = Syllable Stacks; TT = Target Tracker

At the end of each intervention session, participants will complete the BrainHQ Task Load Index (TLX). At the end of Intervention Session 3, subjects will be given a Blinding Questionnaire which asks whether they thought they received active or sham treatment.
Post-Intervention Session (Visit 7)
At the post-intervention session, participants will complete the NIH QOL, NSI, ISI, SDMT, and NAB Attention Module. Subjects will also be given a Blinding Questionnaire which asks whether they thought they received active or sham treatment.

Participants will then be fitted to EEG and eye tracking equipment to assess neural dynamics during the Fusion task. Participants who undergo MRI scans will then be escorted to NMCSD Radiology to have their final MRI scan. The visit length is expected to be approximately 145 minutes.

Research team members should schedule their post-assessment session six-weeks later before the post-intervention session ends.

Six-Week Follow-Up Session (Visit 8)
This last visit occurs six-weeks after completion of the tDCS and cognitive training intervention. Participants will not receive stimulation. They will instead be assessed via paper assessments (NIH QOL, NSI, ISI, SDMT, and NAB Attention Module) and then fitted to EEG and eye tracking equipment to assess neural dynamics during the Fusion task. If desired, they can receive a letter of appreciation for their participation in the study. The visit length is expected to be approximately 70 minutes.

INSTRUMENTS
List of assessments
Contact Information Form. The contact information questionnaire requests general information such as name, address, phone, and email which will be collected at the beginning of the study after informed consent is attained. All identifying information will be matched to the participant via ID code number and be stored in a locked and secure location, separately from study data, as described elsewhere. The contact information form takes approximately 2 minutes to administer.

Baseline Interview. A baseline interview will be conducted to obtain information regarding demographics, military status, educational history, sleep habits, medical history, and supplemental questions related to TBI history. This information will be used for the purpose of confirming study eligibility related to TBI and other inclusion/exclusion criteria as well as for secondary data analyses. This information will be used in conjunction with the Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) to determine TBI history and severity. The baseline interview takes approximately 5 minutes to administer.

Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID). The OSU TBI-ID is a structured interview used to assess the extent and severity of TBI history. The examiner will review the cause, symptomology, treatment, and other relevant information for each potential TBI incident reported by the participant. The interview may be completed using a digital source document. Participants who are unable to provide adequate information for the examiner to determine whether that they meet inclusion/exclusion criteria (e.g., individuals with a TBI of uncertain severity) will be excluded from primary analyses. The OSU TBI-ID takes approximately 15 minutes to administer for patients with a history of TBI, and approximately 5 minutes for controls.

tDCS Symptom Rating Questionnaire (SRQ). We will utilize a pre-post symptom rating questionnaire similar to that described in Thair, et al. (2017). Common symptoms (e.g. Headache, scalp irritation, tingling, etc.) are rated by the participant on a 4-point Likert scale (0-3). Furthermore, the participant rates their belief that the
reported symptoms are related to tDCS on a 5-point Likert scale (1-5). This assessment will be completed before and after each tDCS session.

NIH Toolbox Quality of Life Assessment (NIH QOL). The NIH QOL Questionnaire to assess quality of life with regard to cognitive, social, emotional, and behavioral abilities (49 questions).

Neurobehavioral Symptom Inventory (NSI). The NSI is a 22-item self-report questionnaire which assesses symptoms of post-concussive syndrome which individuals may experience after sustaining a MTBI. The questionnaire is well-validated in research studies investigating MTBI and PTSD in military populations. The Mild Brain Injury Atypical Symptoms (mBIAS) scale is a 5-item self-report measure designed to evaluate symptom exaggeration. The items form the mBIAS are embedded within the NSI to create combined NSI/mBIAS measure. The NSI takes approximately 10 minutes to administer.

Insomnia Severity Index (ISI). The ISI is a brief 7-item self-report questionnaire which assesses the severity of both nighttime and daytime components of insomnia. Individuals report on the nature and impact of sleep problems and difficulties in the last month using a 5-point Likert scale (e.g. 0 = no problem, 4= very severe problem), yielding a total score from 0 – 28. There are three versions of the scale for patients, clinicians, and significant others. The patient questionnaire will be used and is well-validated in clinical patients (https://academic.oup.com/sleep/article/34/5/601/2281474).

Symbol Digit Modalities Test (SDMT). The SDMT is a brief measure requiring visual scanning, attention, and working memory on a timed task. The task is a simple substitution task that gives the examinee 90 seconds to pair specific numbers with given geometric figures. The measure has been shown to be sensitive to brain damage and is especially sensitive to working memory and attention weaknesses/deficits. Raw scores are generated and converted to Z scores based on established norms.

NAB Attention Module. The attention module provides a marker of an individual’s attentional capacity, working memory, psychomotor speed, selective attention, divided attention, and information processing speed through 4 separate subtests. Scores are converted to standard scores based on established normative criteria.

Blinding Questionnaire. The three-question assessment asks participants whether they believed they were in the active or sham/placebo conditions, their level of rated confidence in their answer, and to provide open feedback on factors that influenced their answers. The questionnaire is adapted from Bourton et al. (2005) and their work assessing successful blinding in randomized controlled trials.

DATA MANAGEMENT
All hard copy and electronic data will be coded by study ID and stored in secure locations at NMCSD to which only authorized research staff, IRB personnel, DVBIC HRPP personnel will have access, including locked file cabinets and password-protected computers under the control of approved project personnel, and secure network storage maintained according to DOD specifications.

Research data will be stored in a different locked file cabinet from identifiers (for hard copy identifiers).

A password-protected electronic master list with the patient’s full name, DOB, and study ID number will be maintained separately from study data in a secured, fire-walled protected computer in NMCSD and/or with restricted access to only the PI and specific research personnel involved in the study.
All research documents and protocols will be kept in accordance with Defense Health Agency policy. As the need arises, paper documents may be transferred to a Command-approved Records Management Facility.

DATA ANALYSIS

Sample Size and Power Analysis
To our knowledge, there are no studies that have performed multiple session, active tDCS with cognitive training in chronic mTBI patients. However, several related studies provide general effects from which we can estimate an appropriate sample. Meta-analyses of healthy participants undergoing tDCS show that samples between 10-30 participants yielded small to moderate effects on (Hedge’s $g = .20$, 95% CI [.02, .38]) \(^{49}\). Comparatively, meta-analytic review of studies with neuropsychiatric patients receiving single tDCS sessions had similar sample sizes ($n = 9-22$) with significant effects for accuracy (Cohen’s $d = .22$, 95% CI [-.04 to .40], $p < .05$), but not for reaction time (Cohen’s $d = -.15$, 95% CI [-.30 to .01], $p = .065$) \(^{51}\). A single study with repeated tDCS sessions demonstrated enhancement on working memory tasks in healthy participants with a sample size of 27 per condition to large effect (Cohen’s $d = .70$).

Specific to TBI, Ulam et al. used a smaller sample size ($n = 13$ per condition) for 10-weeks of tDCS sessions with no cognitive training, and still yielded significant associations between EEG and neuropsychological performance. In the pilot study conducted by VA Minneapolis, the investigators were able to recruit approximately 30 participants per year with attrition rates of 10% and 16% at the 1 month and 2-month follow-up sessions, respectively. Results of their study yielded significant findings in a Veteran population (see 1.10d).

For an Active Duty service population seeking services for mTBI, we believe a goal of 60 recruited participants with a conservative estimate of 20% attrition over the entire period would yield 48 completed participants in the final study cohort ($n = 24$ active tDCS, $n = 24$ sham). These numbers reflect the goal of obtaining a comparable number of subjects from similar studies assessing multi-session, active tDCS with both offline and online cognitive training, in addition to feasible recruitment from the NMCSD clinic. Data from this study sample will be used to estimate effect sizes for follow-up larger scale research.

Aim 1. Compare effects on attention and working memory of active vs. sham tDCS paired with attention and working memory tasks.

Analyses will model statistical relationships between group status (active treatment vs. sham), clinical characteristics, and indicators of neural and cognitive function. Differences in tDCS SRQ will be evaluated between group status and pre-post tDCS sessions.

Analyses of our primary neuropsychological outcome assessments (i.e., OSU-TBI-ID, NIH Toolbox Quality of Life Assessment, Neurobehavioral Symptom Inventory, Insomnia Severity Index, Symbol Digit Modalities Test, NAB Attention Module) and Fusion Task data will be also be assessed using repeated measures analyses of variance, between group status and pre-post intervention. Demographic indicators that are known to be potential confounds to neuropsychological performance (e.g., age and education), and other potential confounds like gender, race/ethnicity, rank, etc., will be evaluated to assess their potential effect on our outcomes. If identified as a significant confound, they will be included as covariates within our analyses.

In all cases, post hoc $t$-tests will be conducted when significant findings are present in ANOVA tests. Multiple testing based on the number of tasks being investigated can increase the risk of type I error. For this reason, methods will be applied (e.g., false discovery rate) to reduce the risk, with results reported with and without adjustment for multiple testing.\(^{88}\)
Aim 2. Compare effects on brain activity changes between active vs. sham tDCS paired with attention and working memory tasks.

Repeated measures analysis of variance (ANOVA) will be conducted for each EEG outcome extracted from the data as described in “Electroencephalogram (EEG) Acquisition and Data Extraction”; EEG/ERP outcomes will be the dependent measure, with group status as a between-subjects factor and pre and post evaluation as a within-subjects factor.

fMRI analysis will be performed using FSL’s fMRI analysis tools FEAT. Data will be corrected for magnetic field inhomogeneities using the field maps collected for each participant using FSL’s FUGUE utility for geometrically unwarping EPI scans. Data will then then be pre-processed using standard steps, in the following order: motion correction using a rigid-body alignment to the middle volume of each run, slice-timing correction using Fourier-space time-series phase-shifting, skull removal using FSL’s BET brain extraction tool, 5mm FWHM spatial smoothing, and highpass temporal filtering using Gaussian-weighted least-squares straight line fitting with a sigma of 60s. Finally, temporal autocorrelation was removed using FSL’s pre-whitening algorithm.

T1 image skull removal will be performed using the BET brain extraction tool with a fractional intensity threshold setting of 0.4 and specifying the voxel that represented the approximate center of the brain for each participant. FLIRT will then be used to register the functional images to the skull-stripped MPRAGE using its boundary-based registration (BBR) algorithm. The MPRAGE will be registered to the standard MNI atlas with a 12 degrees of freedom affine transformation.

Resting-state fMRI images will be motion corrected and temporally filtered using a band-pass temporal filter with a high-pass cutoff of 0.01 Hz and a low-pass cutoff of 0.1 Hz. Data will then be smoothed using a 5mm Gaussian kernel. Next, mean white matter and CSF signals across time are calculated for each participant by segmenting the T1 volume using FSL’s FAST segmentation tool and transforming the resulting masks into the resting state functional space. CSF signal, white matter signal, and motion parameters are regressed out of the resting state data, and subsequent analyses are performed on the residuals. Time courses for regions of interest are then extracted for each participant. Pearson correlation coefficients can then be computed between all ROIs and converted into z-scores using Fisher’s transformation.

POTENTIAL RISKS AND BENEFITS

Risks

Assessments

Regarding remaining research risks, participants may experience fatigue and/or boredom while completing the interviews, questionnaires, and cognitive tests. Some participants may also experience mild anxiety, frustration, and/or stress while reporting on their psychiatric symptoms, during assessment procedures if a cognitive test proves difficult for them, and/or during the course of behavioral intervention. It is possible that some participants might not experience symptomatic relief from the intervention. Lastly, there is a risk that a small minority of participants may become distressed during the process of completing the study. These individuals will be reminded that they do not need to answer any questions or complete any tasks that make them feel uncomfortable, and reminded that they may discontinue participation at any time if they wish.

MRI – Optional

The risks associated with MRI scans are:
Projectiles: Objects with magnetic properties can be pulled into the magnet and turn into projectiles. To minimize this risk, we ask that subjects remove all metallic items (watches, cell phones, hair pins, etc.) prior to entering the scanner and by controlling access to the scanner.

Claustrophobia: The scanner is a long narrow tube that may cause some people to feel uncomfortable due to a fear of small, enclosed spaces.

Hearing Damage: The noise generated by the operation of the scanner during the study is loud enough to cause hearing damage if you do not wear hearing protection. Hearing protection is required and is provided by the investigator.

Nerve Stimulation: Some people experience localized tingling, twitching, or muscle contractions during MRI scans. This is expected, but if it is uncomfortable please notify the investigator.

Disruption of Devices: Some devices can be damaged by magnetic fields and should not be brought into the scanner room. This includes some implanted devices such as pacemakers, cochlear implants, insulin pumps, nerve stimulators, etc. If you have any implanted device, notify the investigator.

Heating of Devices: The radiofrequency waves used in MRI can heat conductive materials such as metal implants (screws, plates, rods, wires, artificial joints, etc.), certain tattoo inks, certain clothing fabrics, jewelry, medication patches, wigs, etc. You will be asked to remove these items if possible. If they cannot be removed, you will be asked to provide more information to allow MRI staff to be able to make determination about the safety of proceeding with the scan.

EEG
Some subjects may find the electrode cap uncomfortable. We will describe the procedure in detail before we begin and advise participants that we can stop at any time and remove the cap very quickly.

tDCS/Intervention.
The risk of harm from tDCS procedures following standard safety guidelines are minimal with no reports of serious adverse effects of injury following large review. Some participants may experience mild side effects, such as low-grade sensations of mild tingling, fatigue, and slight itching at the onset of stimulation, with less frequent symptoms being slight burning, or mild pain. Some participants may also experience mild headache, nausea, or insomnia, though the prevalence of these symptoms remain low. Individuals will be reminded that they do not need to complete any tasks that make them feel uncomfortable and reminded that they may discontinue participation at any time if they wish. We will be utilizing parameters for the modality according to the safety guidelines and instructions of preliminary studies; trained study staff will also administer the treatment sessions.

Data
Although efforts are made to protect your research study records, there is always a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.

Protection against Risk
You may choose to discontinue stimulation at any time during the session if you are experiencing excessive discomfort or side effects.
If we feel it is needed or you request it, we will provide you with referrals to a mental health care provider for evaluation or treatment at your option if a licensed member of the study team judges that you may benefit from these services based upon evidence of mental health difficulties. However, this study is not intended to diagnose or treat any mental health conditions. Non-referral does not imply the absence of a mental health condition.

Alternatives to Taking Part in the Research
If you choose to take part in the study, you will be asked not to partake in other cognitive training until the study is over. You can keep taking part in other treatments that do not involve cognitive training. You can withdraw from the study if you change your mind.

Choosing not to participate in this research study is also an option. If you choose not to take part in this study, you may already be eligible to receive other cognitive treatments from your medical providers. Talk to your doctor if you have any questions about other cognitive treatments that may be available to you.

Benefits
Your participation in this research may or may not be of direct benefit to you personally. However, others may benefit in the future from the information learned during this study. The treatments used in this study are designed to help people with mild TBI. Also, results of this study may help the investigator develop tools for the improved treatment of mild TBI.

Incidental Findings
There is a possibility that while reviewing your test results we may see an abnormality that we did not expect to see in this study. This is what is called an “incidental finding.”

We will let you know if we see such an incidental finding. Depending on the type of incidental finding, we may contact you by phone. In the case of a potential serious emergency, the researcher will inform you right away.

You do not have an option to decline receiving information about an incidental finding. A qualified person (usually a member of the research team) will talk to you if there is an incidental finding.

We will also give information about this incidental finding to your primary doctor or we will refer you to an appropriate doctor for further evaluation.

An incidental finding may cause you to feel anxious

Since an incidental finding will be part of your medical record, you could face greater difficulty in getting health or life insurance

The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be your responsibility. If you are a DoD beneficiary, you will have access to care through standard Military Health System and TRICARE procedures.

Privacy, Confidentiality and Information Security
Records of your participation in this research study may only be disclosed in accordance with state and federal law, including the Federal Privacy Act, 5 U.S.C.552a, and its implementing regulations. DD Form 2005, Privacy Act Statement - Military Health Records, contains the Privacy Act Statement for the records. A copy of DD Form 2005 can be given to you upon request, or you can read on-line at:
The research team will keep your research records. These records may be looked at by staff from the NMCSD IRB, DVBIC, General Dynamics Information Technology (GDIT), Defense Health Agency (DHA), the Institutional Review Board (IRB), and the DoD Higher Level Review as part of their duties. These duties include making sure that the research participants are protected. Confidentiality of your records will be protected to the extent possible under existing regulations and laws but cannot be guaranteed.

Procedures to protect the confidentiality of the data in this study include but are not limited to: Your research records will be labeled with a code number. The list that matches your name with the code number will be kept in a locked file in the research team’s office. Any research records that identify you will be kept only as paper records in a secure location, or as files behind the secure computer firewall. Audio recordings of treatment sessions will be stored on a secure server and will be accessed by study investigators for the purposes of rating the delivery of the treatment. Identifiers might be removed from the identifiable private information that are collected. After that removal, the information could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.

Your data will be sent to the Federal Interagency Traumatic Brain Injury Research Informatics System (FITBIR). All data that is sent to FITBIR will be completely free of any identifying information such as names and unique subject identification numbers.

Researchers will make every effort to protect your privacy and confidentiality; however, there are risks of breach of information security and information loss.

By signing this document, you give your permission for information gained from your participation in this research study may be published in literature, discussed for educational purposes, and used generally to further science. You will not be personally identified when your information is shared in these ways; all information will de-identified.

Complete confidentiality cannot be promised for military personnel, because information regarding your health may be required to be reported to appropriate medical or command authorities to ensure the proper execution of the military mission, including evaluation of fitness for duty.

Research Staff, DVBIC, GDIT, DHA, IRB, and the DoD will have access to your records and agree to safeguard your protected health information by using and disclosing it only as permitted by you in this consent or as directed by state and federal law.

Reportable Events

**Rare but serious (Event Rate < 1%)**: Potential breach of privacy or confidentiality.

**Less Likely (1% ≤ Event Rate < 5%)**: There is a risk that a small minority of participants may become distressed during the process of completing the study.

Reportable Events include adverse events (AE), serious adverse events (SAE), unanticipated events, protocol deviations, and protocol violations as defined by the NMCSDD Guidebook.

Events which are classified as not serious and are unexpected (not outlined in the protocol and consent form) will be submitted to NMCSDD IRB within five working days of discovery. Those classified as SAEs (even if expected) will be submitted to the IRB within one business day of discovery. The NMCSDD IRB Chair will be
notified of all SAE submissions via e-mail upon submission. AEs will also be submitted in summary form, by completing the AE log, at the time of continuing review.

A **protocol deviation** is defined in the NMCSD Guidebook “as any change, divergence, or departure from the study design or procedures of a research protocol and that has not been approved by the IRB.” Protocol deviations will be submitted in summary form, by completing the deviation/violation log, for acknowledgment at the time of continuing review.

A **protocol violation** is defined in the NMCSD Guidebook as “a deviation from the IRB approved protocol that may affect the subject’s rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data.” NMCSD IRB will be notified in writing within one working day of discovery of a protocol deviation. NMCSD IRB Chair will be notified of all protocol violation submission via email, upon submission.

The PI will also submit any reportable event documentation mentioned above to the Defense Center of Excellence (DCoE) HRPP Office at the time of notification to NMCSD IRB. The PI will also provide IRB determinations to DCoE HRPP Office.

The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO. Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

Any deviation to the protocol that may have an adverse effect on the safety or rights of the subject or the integrity of the study will be reported to the USAMRMC ORP HRPO as well as the USUHS IRB as soon as the deviation is identified.

Major modifications to the research protocol and any modifications that could potentially increase risk to subjects will be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the USAMRMC ORP HRPO for acceptance.

A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available.

The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning this clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements that relate to this clinical investigation or research will be reported immediately to USAMRMC ORP HRPO.

Any protocol deviations during the course of the study will be promptly reported to IRB and sponsor if applicable, through the medical monitor of the protocol if applicable. Examples of deviations include but are not limited to variances from the treatment schedule for an individual patient, failure to use the most current consent form, and/or incomplete or lost records.

All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study will be promptly reported by phone (301-619-
2165), by email (hsrrb@amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

PROJECTED TIMELINE
This project will take two years (24 months) to complete. Months (1-3) of the project will be dedicated to the recruitment and training of new personnel, full implementation of all procedures, and beginning recruitment of research participants. Months (4-20) will be the data collection phase; data curation and pre-processing will occur on a continuous cycle. Months (21-24) will focus on data analysis, and manuscript preparation.

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DISSEMINATION AND TRANSLATION PLAN
Findings from this study will be disseminated via presentation at scientific conferences, manuscript publication, and communication with clinical providers both locally at the Naval Medical Center San Diego and across the DVBIC network. Relevant conferences include the Military Health System Research Symposium (MHSRS; in August, annually), Society of Biological Psychiatry meeting (in May, annually), American Congress of Rehabilitation Medicine (in April, annually), American Academy of Clinical Neuropsychology (in June, annually) and the International Neuromodulation Society (in June, annually). Any potential translational findings from this project will be discussed with the interdisciplinary treatment team at NMCSD TBI Program, as well as with researchers and clinicians in the DVBIC network.

PERSONNEL
Lars Hungerford, PhD (30% effort) is the Senior Clinical Research Director for DVBIC at the Naval Medical Center San Diego. He has experience with the assessment and investigation of TBI and related disorders (e.g. PTSD, insomnia, depression, etc.), which are known to negatively impact neurocognitive functioning. He is a subject matter expert on TBI and has expertise in the use of psychophysiological brain biomarkers and neuromodulation techniques. Dr. Hungerford will direct the overall study and be responsible for oversight of cognitive training and tDCCS administration, as well as data analysis and manuscript preparation.

Anna Nunes, MS (50% effort) is a DVBIC Research Associate at NMCSD. She will primarily conduct all aspects of the study including recruitment, consenting and assessment of study participants, implementing intervention, maintaining organization of study related documents, and data entry and management.

Mark Ettenhofer, PhD (15% effort) is a Research Neuropsychologist for DVBIC at NMCSD, an Assistant Professor of Medical and Clinical Psychology at Uniformed Services University, and a Principal Investigator at the University of California, San Diego and the VA San Diego Healthcare System. He has experience conducting TBI

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clinical trials within DoD environments, and will provide assistance with study design, data analysis, and manuscript preparation.

Casey Gilmore, PhD (10% effort) is Research Scientist for DVBIC at the Minneapolis Veterans Affair Medical Center. Dr. Gilmore specializes in abnormal brain activity underlying psychopathology, with extensive experience with advanced imaging processes, including electroencephalography (EEG) and tDCS in populations with schizophrenia, program gambling, substance use, externalizing disorders, and blast-related mTBI. He will serve as expert consultant for tDCS + cognitive training intervention of the study.

Jamie Hershaw, PhD (10% effort) is a DVBIC Research Scientist at Fort Carson, CO specializing in psychophysiological methodology. She will be the expert consultant on EEG/ERP acquisition, pre-processing, data extraction and analysis, and results interpretation in the study.

Sarah Gimbel, PhD (15% effort) is a Research Scientist on the DVBIC research team at NMCSD. She has been working in the field of cognitive neuroscience for 14 years and published ~20 manuscripts where she has designed, implemented, and analyzed fMRI data in conjunction with psychophysiological and clinical measures within interdisciplinary research studies. She will organize and conduct all aspects of MRI data collection and data analysis and prepare the MRI data for dissemination.

Jenna Trotta, MS (10% effort) is a Research Psychometrist for DVBIC at NMCSD. She will assist the research coordinator in all aspects of the study including recruitment, consenting and assessment of study participants, maintaining organization of study related documents, and data entry and management.

Angelica Aguirre, MS (10% effort) is the Research Coordinator for DVBIC at NMCSD. She will coordinate all aspects of the research related to subject assessment including recruiting/consenting patients, scheduling assessments, collecting data from subjects, and organizing the study cohort data. In addition, the research coordinator will assist with data organization, analysis and assembly of materials to assist with dissemination of research findings related to the project.

Josh Kenton, PhD (5% effort) is the Head of the NMCSD TBI Department and a clinical neuropsychologist. He has developed substantial clinical experience and expertise in the diagnosis, treatment and long-term care of Veterans and Active Duty Service Members with traumatic brain injury. Given his experience, access to NMCSD TBI patient populations, knowledge, and leadership role, he will be instrumental in the successful completion of the proposed project by providing expert consultation on traumatic brain injury to the local research team.

ENVIRONMENT
Research will be conducted at the Naval Medical Center San Diego (NMCSD) TBI Program. NMCSD is a flagship Navy MTF that is highly supportive of research. There are nearly 180 investigators at this institution conducting research. The NMCSD TBI Program provides interdisciplinary care to nearly 400 Active Duty Service Members per year from California and Arizona. It supports basic, translational, clinical, and outcomes/health services research, with full-time research support staff, state-of-the-art laboratories, and abundant common service equipment relevant to this project. The medical center uses the Department of Defense (DoD) electronic medical record system, AHLTA, which allows ready retrieval of relevant clinical and epidemiological data. NMCSD has an ample medical library, with interlibrary loan service. If needed, emergency medical and psychiatric services are also available through Urgent Care or consultation with an on-call psychiatrist. In addition, there are institutional resources to support research activities, including statistical consultants, information technology support, media production, and library services.
Neuroimaging Resources. MRI scan sessions will take place at the Navy Medicine Radiology Department at NMCSD. The hospital’s center has 3 Philips Ingenia 3T scanners, running R5.3.1 software. There are both 16 and 32 channel head coils available for research use. The DVBIC research team is allotted 2 sessions each week to schedule appointments exclusive for research participants. Coordination with the Radiology team will be conducted by Dr. Gimbel.

Dedicated Research Space. Drs. Hungerford, Ettenhofer, Gimbel, and Ms. Anna Nunes all have office space at the Naval Medical Center San Diego. The PI and Co-Investigators have PC computers equipped with laser printers and standard word processing, spreadsheet, and database software, as well as access to statistical programs (e.g. Matlab, SPSS, SAS/STAT). All NMCSD office computers have access to the DoD electronic medical record software as well as scheduling and Internet software. Two clinical offices within NMCSD encompassing approximately 250 square feet will be dedicated to the assessment of study patients.
**BUDGET/INVENTORY**

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