rTMS to Improve Cognitive Function in TBI

NCT 02152540

IRB-Approved 12/11/2018

02. Research Plan
I. BACKGROUND AND SIGNIFICANCE

A. Cognitive Dysfunction in Mild and Moderate Traumatic Brain Injury (TBI)
The proposed study will evaluate the safety, durability and efficacy of repetitive Transcranial Magnetic Stimulation (rTMS) as a promising non-invasive therapeutic treatment for executive function (EF) deficits seen in 40 mild to moderate Traumatic Brain Injury (TBI) Veterans.

Many returning OEF/OIF Veterans with concussion histories report cognitive problems that may last for months or even years (Schneiderman et al., 2008; Hoge et al., 2008). Although deployment itself can be associated with cognitive problems (Vasterling et al, 2006), having co-morbid conditions such as post traumatic stress disorder (PTSD) and depression may prolong the symptoms of TBI resulting in lowered attention, processing speed, learning and memory (Nelson et al., 2012; Caeyenberghs et al., 2012). Strong evidence also suggests that a history of TBI increases risk for developing PTSD (Eckart et al., 2011). Significant progress has been made towards understanding the pathophysiology and neuropsychological changes associated with the acute and long term sequelae of TBI, including its complicated relationship with PTSD (Brenner et al., 2011; Hallbauer et al., 2009; Villamar et al., 2012). However, few studies have addressed what mechanisms of TBI may be responsive to therapeutic treatment.

The most common cognitive difficulties faced by Veterans with TBI include executive function deficits such as impaired attention, verbal fluency, poor planning, reduced working memory, and mental flexibility (Godefroy et al., 2003). A survey of Army infantry who suffered from TBI reported that 31.4% complained of concentration problems and 24.6% complained of memory problems (Nelson et al., 2012). A large literature confirms that Dorso Lateral Prefrontal Cortex (DLPFC) is involved in inhibition, planning and set-switching - key components of executive function (Vanderhasselt et al., 2006). Deficits in executive function following mild TBI (mTBI) are also associated with injury to the axons and involve the DLPFC (Lipton et al., 2009). In fact, patients with focal lesions in this brain region performed significantly worse than controls on the Trail Making Test (TMT: primary outcome measure) suggesting impaired cognitive set-shifting (Yochim et al., 2007). Moreover, control participants performed significantly better on TMT than patients with mTBI (Brooks et al., 1999). We hope to demonstrate improvement of this deficit in Veterans with mild and moderate TBI through rTMS treatment. Additionally we would also report on the efficacy of using functional brain connectivity (thru advanced neuroimaging) as a biomarker to capture this improvement in executive function.

Previous studies have documented the relationship between injury severity, cognitive impairment and functional status (Bush et al., 2003; Senathi-Raja et al., 2010). In fact, Bercaw et al, (2011) reported that neuropsychological performance at year 1 post-injury predicted functional outcomes in year 2. Although reports of mild TBI patients returning to baseline functioning one year post-injury have been documented, 7% to 33% of these patients experience persistent symptoms (Belanger et al., 2005). Note that regardless of injury severity, one of the most frequently reported post-TBI sequelae is cognitive dysfunction (e.g, memory problems and executive function: Terrio et al., 2009; Senathi-Raja et al., 2010). Among these patients there is often little correlation between subjective (e.g, self-report) and objective markers (eg, neuropsychological test performance) of such dysfunction (Brenner et al., 2011). Moreover these cognitive complaints have been associated with poorer psychosocial functioning (eg, return to work; Benedictus et al., 2010).

B. Overview of rTMS in Cognitive Dysfunction in mild and ModerateTBI
Repetitive TMS is a method of delivering therapeutic, non-invasive brain stimulation. While not yet utilized in TBI research on a large scale, rTMS is well suited for this pilot project given the clinical and research expertise in rTMS trials for various other common Veteran complaints (e.g., team of 5 MD's, 1 RN, 3 clinical neuropsychologists and 2 neuroimaging researchers in the VA; FDA approvals for Investigational Device Exemptions (IDE)). rTMS is currently being used at the VA Palo Alto and Stanford University in the treatment of: pain (VA Rehabilitation grant funded: PI: Dr. Ashford & Co-I/Co-Protocol Director: Dr. Adamson), depression (VA Co-op studies funded, PI: Dr. Rosen; Co-op studies funded, PI: Dr. Yesavage), and PTSD (NIH funded project: Dr. Etkin). At present it is an FDA-approved for treatment for major depression (Oreardon et al., 2007; George et al., 2010: Dr. George, current consultant). A recent VA study reported improvements in PTSD and related symptoms in Veterans with PTSD who received rTMS (Watts et al., 2012). Also of relevance in our TBI Veterans, a major industry trial of rTMS in Treatment Refractory Major Depression (TRMD) has

been completed. This randomized controlled trial involved 301 medication-free patients with TRMD and excluded patients dual-diagnosed with co-morbid substance abuse (past year) or PTSD. Response and remission rates were significantly better in rTMS than in controls at the end of 6 weeks treatment, but results were smaller and not significantly better after 4 weeks treatment. Because the 4 week outcome was the a priori defined primary end point, the FDA Advisory panel reviewing this study did not accept this result as adequate support of this new indication for rTMS. (However, the most recent data concerning the 12 month durability of a TMS antidepressant effect are quite good, with over 90% retention of remission 12 months later in a treatment resistant group (Demitrack, 2013). This compares to a 50% relapse rate in similar populations who are treated with ECT, or even worse outcomes in patients treated with medications (STAR*D). We are now rediscovering how exercise, practice, and stimulation can cause plastic changes in the brain (Colcombe et al, 2006). In sum, the only way to discover whether there are acute or more durable effects with rTMS treatment for TBI is to do the proposed study.)

(Rationale for rTMS use in EF improvement: Repetitive TMS treatment can induce neuronal long-term potentiation (Wang et al 2011) involving brain-derived neurotrophic factor (BDNF) resulting in synaptic repair (Cheeran et al., 2008; Lu et al., 2013). Pape et al (2006) review the evidence for rTMS as a possible intervention for TBI-induced cognitive dysfunction in patients with Parkinson's disease and strokes. So far, improvements after rTMS treatments (stimulation site: DLPFC in neurobehavioral outcomes (Pape et al., 2009) and executive function (Pachalska et al., 2011) have only been reported in severe TBI patients. Case studies (Bonni et al., 2013) have found rTMS to lead to improved cognitive functioning in patients with TBI. A recent review of rTMS studies across various mental illnesses strongly suggests its use in TBI to promote recovery and minimize disabilities (Demirtas-Tatlided et al., 2012). Stimulation of the left dorsolateral prefrontal cortex (DLPFC) has led to improvements in major depressive disorder. This brain area has also been shown to be involved in executive functioning (Yochim et al., 2007), and we thus hypothesize that stimulation of this area will lead to concomitant improvement in executive functioning).

The proposed pilot study is an advance and necessary for the VA because: 1) It will incorporate dual-diagnosis TBI (mild and moderate) patients including patients with PTSD. These dual-diagnosis patients are usually excluded from industry and National Institute of Health trials and as such the proposed study is unique in that it will address the patient that providers encounter in the VA system specifically. 2) It will focus on improvements in cognitive dysfunction - a major complaint for many Veterans who, may not seek medical care and which will impact their cognitive health and independence as they grow older. 3) Furthermore, unlike industry trials, the proposed study will use a sham rTMS procedure that will be more difficult to distinguish from the actual rTMS.

C. rTMS Physics

rTMS induces firing in cortical neurons by producing brief pulses of an intense magnetic field, which ultimately lead to neuronal summation and depolarization (Bohning, 2000). An rTMS machine stores electricity in large capacitors, which when discharged, transiently creates about 3,000 Amps of current. High-intensity, but extremely brief (2 ms) electric power of approximately 5 million watts (5MW) is quickly switched on and off by thyristors, regulating the electromagnetic coil through the discharge of large capacitors. (Barker, 1989;Bohning et al., 1997; Davey et al., 1991; Roth et al., 2002). It is these large but transient electric currents that create a powerful magnetic field, up to 2 Tesla, in accordance with the principles described in Maxwell's equations and Faraday's law. Thus, the magnetic field is significantly greater than that associated with common permanent magnets. The rapidly pulsing magnetic field (~30KT/s) then travels across the scalp and skull and induces an electric field within the aqueous extracellular matrix of the brain (~30V/m). The resultant transmembrane potential leads to summation and, at sufficient doses, an action potential (Bohning, 2000). Hence, with rTMS, there is no direct passage of electrical currents through the brain, as occurs in Electro Convulsive Therapy (ECT) – a much more invasive technique.

An rTMS magnetic field consists of pulses of only 2 ms in duration, which is of significant strength only directly under the rTMS coil. For these reasons, it is accepted by most rTMS researchers that rTMS produces its effects solely through the production of electrical currents in the cortex of the brain, and secondary neuronal network augmentation. Because magnetic fields induced by rTMS decline rapidly with distance from the coil, current rTMS coils are only able to directly stimulate the superficial cortex, and are not able to produce direct electrical stimulation deep in the brain (Bohning, 2000; Roth et al., 1994; Roth et al., 2002). Deep brain structures are influenced secondarily through the activation of cortical-subcortical tracts.

D. General rTMS Procedure and Determination of Motor Threshold (MT)

An rTMS procedure is non-invasive, and no anesthesia is required. Participants are awake and alert as a hand-held electromagnetic coil is placed over the head (See Fig. 1). Participants typically notice only a loud clicking noise, and tingling sensation on the scalp. This scalp sensation results from the sound wave emitted as electricity passes through the coil, and from the rhythmic tensing of superficial nerves and scalp muscles. Routine rTMS is usually mildly uncomfortable, but in some cases, when applied over certain peripheral or cranial nerves, can be painful. (Note: Our stimulation site, DLPFC is approved by FDA for treatment of depression). The amount of electricity passed through the coil (and hence the power of the magnetic field generated) necessary to induce cortical firing varies from person to person, and also from one brain region to the next (Stewart et al., 2001). For Sham control see section IV.E.

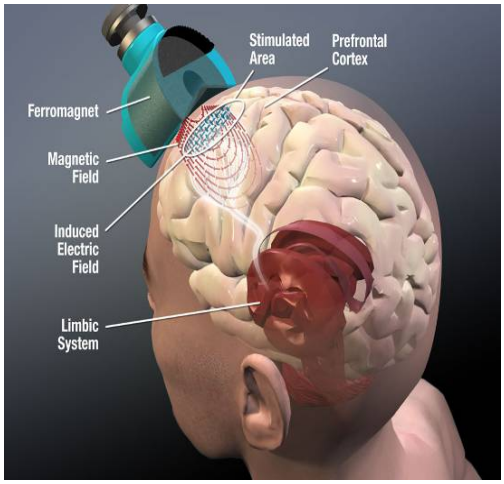


Fig. 1. Diagram of simulated rTMS delivery (Machine, and area of stimulation (DLPFC) used in the proposed pilot study.

To determine the necessary level of power that must be used, the establishment of a “motor threshold” (MT) is the most commonly employed technique (Kiers et al., 1993; Pridmore et al., 1998). The MT is usually defined as the minimum amount of electricity needed to produce movement in the contralateral thumb, when the coil is placed in the appropriate spot over the primary motor cortex (Pascual-Leone et al., 1993). rTMS patients sit upright or slightly reclined, wear earphones, and close their eyes and rest during a procedure. The patient’s head is sometimes restrained in a headrest, while the rTMS coil is initially positioned by the administrator, and held in place against the scalp using a coil-holder. Because rTMS treatment produces no significant cognitive or physical side effects, patients are typically treated on an outpatient basis, driving themselves to and from their rTMS treatment appointment, and attending to their usual daily responsibilities (but section E for safety concerns and Appendix A for safety/seizure protocol).

E. rTMS Safety especially for Mild and Moderate TBI Veterans

After a decade of research, rTMS is generally regarded as safe and without lasting side effects if established guidelines are followed (Janicak et al., 2008; Machii et al., 2006). There have been no significant cognitive (Triggs et al., 1999; Little et al., 2000), neurological (Nahas et al., 2000) or cardiovascular sequelae reported as a result of rTMS. (see Human Subject Section C for more details).

The primary safety concern with rTMS, in any population, has been the risk of seizure induction. Eight seizures have been reported secondary to rTMS (Wassermann, 1998). These have occurred in a sample size estimated to be over several thousand rTMS treatment sessions. The rTMS community has adopted and widely used the guidelines prescribing a safe interval between pulse trains (Gerloff et al., 1997) and the safety guidelines from a National Institute of Neurological Disorders and Stroke (NINDS) workshop on rTMS. To our knowledge there have been two publications since 1997 describing events during rTMS that might be considered seizures. Conca and colleagues reported a patient who experienced a ‘pseudoabsence seizure’. It is unclear if this was a true seizure (Conca et al., 2000). Bernabeu and colleagues reported on a patient who had a seizure during rTMS. In this case, there was a brief interstimulus interval (Bernabeu et al., 2004). The risk of seizures for rTMS treatment is less than 1%.

How does this impact our study: The current safety guidelines have not been tested for mild and moderate TBI population which is precisely the purpose of this pilot grant. In TBI population, posttraumatic epilepsy is the most common delayed sequelae of TBI. But this incidence is very low (about 5%) in TBI patients with closed head injury (Ropper et al., 2005) who are most likely our mild and moderate TBI patients. In a clinical setting, for example in Polytrauma Transitional Rehabilitation Program (PTRP – VAPA) the expected recovery trajectory for persons with mTBI is full cognitive recovery in 3-6 months following injury. Persisting or worsening cognitive status is often related to other co-morbid psychiatric issues, such as depression and PTSD, chronic pain, sleep apnea (all will be) used as covariates in our analysis). Including persons with moderate TBI in our study would likely allow for examination of rehabilitation treatment effects on cognitive functioning for those who tend to have persisting cognitive difficulties following injury. On PTRP, patients are

often admitted from the acute inpatient rehab unit on anticonvulsant medications if they had a seizure 1 day or more following the injury. Typically, if the patient experienced a seizure immediately at the scene of the incident, they are not considered at a greater risk for subsequent seizures. For those who do not have a history of seizures following injury, they are not considered at a greater risk of subsequent seizures and are not placed on anticonvulsant medications. Importantly, the interval between the head injury and the first seizure varies greatly (Demirtas-Tatlidede et al., 2012*)* and must be considered as a variable for recruitment in this study. Currently PTRP houses patients 2 months to 2 years post TBI. Note, that there is only one case study which performed detailed safety assessments and reported a lack of adverse events in a patient with severe TBI following application of a specific rTMS protocol over 5 consecutive days through 6 weeks (Pape et al., 2009). Our protocol will be highly stringent and will exclude any severe TBI patients (including those with any fractures, metal plates or open head injuries), acute patients or those who have had a concussion within the last 2 months, and those who have a history of seizures of any type.

(F. Multimodal Neuroimaging as a Biomarker for capturing improvement in EF after rTMS)
Insights gained from other patient populations must be translated to TBI patients with carefully characterized deficits (as mentioned above in Section E). (We would like to add multimodal imaging (Diffusion Tensor Imaging (DTI: Fig 2) and resting state fMRI (Fig 3) as possible biomarkers to detect improvement in EF after rTMS treatment). DTI is a novel imaging technique for noninvasive in-vivo visualization of white matter tracts in the brain (Le Bihan et al., 2001). The degree of anisotropy (fractional anisotropy, FA) changes as a function of the degree of fiber tract organization (due to injury or rehabilitation), that is, a reduction in FA values typically indicates histological abnormality (Basser et al., 1996; Rosen et al., 2010). (Functional MRI allows for the investigation of whole brain response to and recovery from patterned stimulation (Eldaife et al., 2011; Pascual-Leon et al., 2011). For example, combining TMS with resting-state fMRI allows clinicians and researchers to experimentally manipulate local cortical responses with patterned stimulation and observing change in network responses (Demirtas-Tatlidede et al., 2012; Fox et al. 2012).The presumption is that brain areas subjected to trauma have had some degree of axonal shearing leading to a general decrease in synaptic activity, regardless of severity of TBI or other co-morbidities. Repetitive TMS treatment can induce neuronal long-term potentiation (Wang et al 2011) involving BDNF resulting in synaptic repair (Cheeran et al., 2008; Lu et al., 2013). This BDNF-based mechanism may lead to improvements in brain connectivity and local brain function that can be captured by altered states of brain at rest. In the sub-acute stage, TMS may influence functional connectivity of certain damaged or sheared circuits providing a therapeutic neuroplasticity mechanism for functional recovery in the chronic or sub-acute stage.) Though rTMS compared with sham stimulation caused no activation changes at the stimulation site (right DLPFC) in schizophrenic patients, increased connectivity within working memory network was observed in an fMRI study (accompanied by shorter reaction time on the task itself) suggesting that plastic changes in prefrontal site have a downstream beneficial effect on executive function (Esslinger et al., 2012). (We suggest that disconnection within the DMN is the underlying cause of the EF impairment. After rTMS treatment that may lead to synaptic repair we expect greater connectivity in the DMN which may serve as a biomarker for improved executive function. To further establish a preliminary understanding of the underlying mechanisms related to rTMS modulation of synaptic repair in TBI we will also look at plasma BDNF in our population (see Table 3).) We propose to collect baseline, post treatment and 6 month follow-up data. We present some preliminary data from WRIISC patients collected at our VA scanner and analyzed at our center in Fig. 2 and Table 1.)

II. Preliminary Data: See Table 1, Fig. 2 & 3.

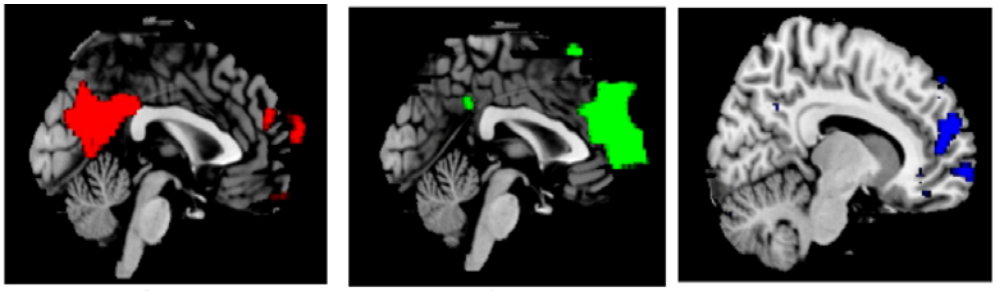
III. Outcome Measures:
A. Primary Outcome Measures: (Improvement in executive functioning will be defined as improvement in performance between baseline and last assessment of $\geq$1 SD on either the Trail Making Test part B, D-KEFS Verbal Fluency and/or D-KEFS Color-Word Interference Test). These tests are given pre, post treatment and 6 month follow-up to all patients (see Table 1 for preliminary data from Polytrauma, VAPA).
B. Secondary Outcome Measures: The selection of secondary outcome measures is based on assessing associated features and co-morbidities understood to typify mild and moderate TBI: 1. Sustained Improvement on executive function: At the end of the 6-month post treatment follow-up, TBI patients who received rTMS would be more likely to continue to have greater “executive function improvement” than patients who received sham rTMS. 2. Secondary consequences of TBI scores on Quality of Life (QOL) scale: will show significantly greater improvement in patients with mild to moderate TBI who received rTMS treatment. 3. Moderators of

Response such as Age, severity of symptoms at baseline, time to injury, type of comorbidity (PTSD, time since injury, sleep, depression substance abuse, (medication use, cognitive exercises, fatigue or any combinations of these), (TBI type), duration of illness and prior treatment resistance (rTMS/ECT): may affect or "moderate" treatment response. 4. Functional connectivity (resting state and DTI): Greater functional connectivity will be observed in hub centers of the Default Mode Network (DMN), particularly the precuneous/posterior cingulate area (shown red in Fig. 3) as measured by resting state fMRI/ DTI at follow-up compared to baseline in those TBI patients treated with rTMS compared to those treated with sham. (5. Mediators of Response to Treatment: to establish a preliminary understanding of the underlying mechanisms related to rTMS modulation of synaptic repair in TBI we will also look at BDNF samples in our population.)

IV. Research Design and Methods:

Patients (*n*)	TBI (S/M)	PTSD (Y/N)	RAT_FA	LAT_FA	LCG_FA	RCG_FA
9	N/A	9 Y	0.39 ± 0.05	0.41 ± 0.03	0.5 ± 0.05	0.49 ± 0.04
4	4 M	N/A	0.42 ± 0.04	0.41 ± 0.04	0.47 ± 0.07	0.46 ± 0.06
28	28 M	28 Y	0.41 ± 0.03	0.41 ± 0.06	0.50 ± 0.05	0.50 ± 0.06
6	N/A	N/A	0.46 ± 0.05	0.44 ± 0.04	0.50 ± 0.05	0.45 ± 0.03

Figure 2: Top, single participant (TBI/PTSD) fiber tracks displayed on T1 image. Chart shows Fractional Anistropy (FA) scores from DTI analysis performed on WRIISC patients (see Table 1) at VAPA (RAT & LAT = Right & Left Anterior Thalamic Tract, purple; LCG & RCG = Right & Left Cingulum, Green). Fibers shown but not FA values are: Inferior Fronto Occipital (Cyan Blue), Inferior Longitudinal (Navy Blue), Forceps Anterior (brown), Forceps Posterior (Orange), Cortical Spinal (Yellow), Superior Longitudinal (red) and Uncinate (mustard yellow).



a b c

Figure 3: Default Mode Network (DMN) activation areas from resting state fMRI using Independent Component Analysis (dual-regression approach).a) Healthy male Veteran (44 yrs); b) Male Veteran with mild TBI (32 yrs); and, c) Male Veteran with mild TBI (72 yrs). Notice that the precuneous/posterior cingulate region (hub center for the DMN) is functionally more connected in healthy young Veteran, less so in the young Veteran with mild TBI and least so in older Veteran with mild TBI.

Patients (*n*)	TBI (S/M)	PTSD (Y/N)	Age (Yrs)	Education (Yrs)	Executive Function
9	N/A	9 Y	49.22 ± 9.61	12 ± 2.78	Trails B: 49.25 ±10.01
4	4 M	N/A	52.50 ± 16.68	16 ± 3.16	Trails B: 44.75 ± 14.93
28	28 M	28 Y	47.57 ± 1271	14.50 ±2.52	Trails B: 44.52 ±12.44
6	N/A	N/A	39 ± 10.08	13.83 ± 1.72	Trails B: 53.40 ± 6.19

(Table 1: Patient neuropsychological data from WRIISC CA (TBI: Severe = S; Moderate & Mild = M); PTSD status by PTSD Check List – Civilian (PCL-C))

A. Study Design: Our hypotheses will be tested in a 2-year randomized double blind clinical trial of rTMS for executive functioning deficits among Veterans diagnosed with mild to moderate TBI following deployment. 40 Veterans diagnosed with mild to moderate TBI (age range 20-65) will be enrolled during 1.5 years in this study. (Inclusion Criteria: 1) We have now determined that since the duration of PTA is a more accurate measure of injury severity (as noted in Brown et al., 2005), only PTA will be used to differentiate between mild and moderate TBI. Our main recruitment resources (VA Polytrauma services) employ clinical interview and O-LOG (a well validated measure of orientation that is a part of the National TBI Model Systems database). An O-LOG score of ≤ 24 on two consecutive days marks the emergence from PTA. As such, duration of time since injury date to O-LOG score of ≤ 24 on two consecutive days will determine the duration of PTA. For those admitted to the Polytrauma clinics after the emergence of PTA, duration of documented LOC will be used to determine the severity of injury (LOC ≤ 30 minutes for mild TBI and LOC >30min but <24 hours for moderate TBI). 2) We will include only those patients who are 1 SD or more below the mean score on Trail Making Test B (TMT B), using the published Heaton et al., (2004) norms, in keeping with the Common Data Elements. This test is included in most neuropsychological (NP) screenings throughout the Polytrauma settings. To limit the burden on the patient and limit practice effects, we will not re-administer TMTB for those patients who have available NP testing within the last 3 months. 3) This

sample will include Veterans with blast or non-blast deployment-related injuries. We will record these differences and use them as a covariate in our analysis. Note: literature does not provide any strong evidence that blast-related injuries are categorically different from other TBI mechanisms after controlling for the influence of psychological distress (i.e., Depression, Stress), in regard to cognitive sequelae on select measures (Belanger et al., 2009; Lange et al., 2012)). Efforts will be made to recruit women and members of diverse ethnic and racial groups. Potential participants will be evaluated on a wide variety of measures including cognitive, neurological and functional parameters (see inclusion/exclusion criteria, Table 2). The primary dependent measures will be significantly greater improvement on executive function measures (see Section III) at the end of the treatment phase, and secondary analyses will be conducted on other variables stated above.

B. Population: The inclusion/exclusion criteria are designed to identify patients with mild to moderate TBI with special attention paid to the safety guidelines discussed in Section I.E.

C. Recruitment: Based on the team established, we will recruit from: War Related Illness and Injury study Center (WRIISC) at VAPA (one of the three in the nation tasked to address complex problems faced by Veterans of the recent wars; PI: Adamson, PhD, Deputy Director Research), Polytrauma VAPA (Co-I: Maya Yutsis, PhD; one of the 5 polytrauma network sites the country and a participating DVBIC site), Memory clinics at VAPA (Co-I: Brian Yochim, PhD) as well as from the surrounding VA clinics. Letters will be sent to patients and providers with information about the study, and a pre-paid response postcard. Flyers will be posted in relevant clinic settings and on the Stanford University Marguerite Shuttle, and study information will be advertised on social media. (We plan to recruit an average of 2.2 patients/month to meet our target enrollment of 40 participants in 18 months).

Table 2: Inclusion/exclusion criteria for participants

Exclusion Criteria	**Inclusion Criteria**
Pregnant or lactating female.	Age 20-65years
Unable to be safely withdraw, at least two-weeks prior to treatment commencement, from medications that substantially increase the risk of having seizures	(History of (Post Traumatic Amnesia < 1 day for mild TBI; 1 day> x < 7days for moderate TBI))
Have a cardiac pacemaker or a cochlear implant	(1 SD or more below the mean score on Trail Making Test B (TMT B))
Have an implanted device (deep brain stimulation) or metal in the brain (see standard MRI exclusion criteria including metal screening section in telephone screen, Appendix A).	Ability to obtain a Motor Threshold (MT) will be determined during the screening process.
Have a mass lesion, cerebral infarct or other active CNS disease, including a seizure disorder.	If on a psychotropic medication regimen, that regimen will be stable for at least 4 weeks prior to entry to the study and patient will be willing to remain on a stable regimen during the acute treatment phase.
Known current psychosis as determined by DSM-IV coding in chart (Axis I, psychotic disorder, schizophrenia) or a history of a non-mood psychotic disorder.	Has an adequately stable condition and environment to enable attendance at scheduled clinic visits.
Diagnosis of Bipolar Affective Disorder (as determined by chart review and intake interview)	For female participants, agrees to use one of the following acceptable methods of birth control: abstinence, oral contraceptive; Norplant,
Current amnesic disorders, dementia, MMSE ≤ 24 or delirium.	
Current substance abuse (not including caffeine or nicotine) as determined by positive toxicology screen, or by history via AUDIT, within 3 months prior to screening	Able to read, verbalize understanding, and voluntarily sign the Informed Consent Form prior to participating in any study-specific procedures or assessments.
Prior history of seizures	
Severe TBI or open head injury	
TBI within last two months or in acute stage	
Participation in another concurrent clinical trial	
(Patients with prior exposure to rTMS/ECT)	
Active current suicidal intent or plan. Patient at risk for suicide will be required to establish a written safety plan involving their primary psychiatrist and the treatment team before entering the clinical trial	

D. Screening, Baseline and Study Assessments: Patients who are screened over the telephone for possible eligibility for the study will be listed on the Patient Screening Log. Note: we will make all our efforts to screen patients for both rTMS and MRI exclusions but as our primary aim is to test rTMS for use in

TBI population, we will enroll participants in the study who are ineligible to be in the MRI scanner but eligible for rTMS treatment. (We estimate that the PI and the Study Coordinator (SC) will do "telephone screens" on 5 potential subjects for every one we can actually treat, and, based on our current recruiting for our rTMS study to treat pain in GW1 Veterans, each of these should take approximately 20 minutes). After the patient signs the Informed Consent Form, the on-site screening procedures and assessments can be initiated. The on-site screening phase will last one week to allow adequate time for all of the assessments to be completed, to assure the patient's capacity and willingness to participate in the study. The Human Studies Subcommittee and/or IRB will review any posters or advertisements used before being posted. It is essential to maintain a flow of patients for screening throughout the 1.5 year recruitment period. Table 3 summarizes the process. The telephone screening and seizure protocol can be found in Appendix A. The list and the frequency of screening, baseline and study assessments are listed in Table 3. Following screening and informed consent participants will be randomized into one of 2 treatment groups: rTMS or sham rTMS. Patients who fail screening may be re-screened at a later time at the discretion of the PI. Randomization to active or sham treatment will be done by random number generator.

D. Duration of the Study: The duration of the study will be two years, with 18 month enrollment period, and the last six month will be strictly for follow-up. 20 participants will be recruited in the first year and 20 will be recruited in the second year. Each participant will be in the trial for a total of approximately (28) weeks (1-2 weeks screening, (2) weeks acute treatment phase (depending on scheduling concstraints) and 24 week (6 month) follow-up phase). (Several FDA approved studies use two 20 min sessions day for rTMS (personal communication with Mark George, MD) which is shorter than what we had originally proposed and our study will now run for 28 total weeks instead of 30 (with only 2 weeks of treatment). Therefore, we may increase retention by reducing the number of visits required). *Treatment Phase*: After randomization, the rTMS administrator will retest the motor threshold (MT). The rTMS administrator will then deliver DLPFC active rTMS treatment or Sham (Control) rTMS treatment for 20 sessions.

Table 3: Screening, baseline and study follow-up assessments and frequencies of tests

ASSESSMENT	**Screening/Baseline**	**Acute Treatment Phase**					**Follow Up**
		2 weeks					
		End of Session Number					
	1-2 weeks	5	10	15	20/last	Immediate post-treatment	6 months
Telephone Screening	X						
Consent	X						
MT Determination	X	X	X	X	X		
Tx Assignment and Randomization date	X						
Demographics	X						
Seizure history	X						
Clinical TBI eval	X						
Medical History	X						
Physical Exam	X					X	X
Mini International Neuropsychiatric Interview (MINI) Plus	X						
Trauma History Questionnaire (THQ)	X						
Mini Mental State Exam (MMSE)	X					X	X
Hamilton Rating Scale for Depression-28	X					X	X
Treatment Outcome in Pain - (TOPS)	X					X	X
Flinders Fatigue Scale	X	X	X	X	X	X	X
Clinician Administered PTSD Scale (CAPS)	X					X	X
PTSD Check-list (PCL)	X					X	X
TBI Identification Method, Short Form (OSU)	X						X
Columbia – Suicide Severity Rating Scale (C-SSRS)	X						
(Test of Memory Malingering (TOMM))	X						
(Labs (blood, saliva) for BDNF plasma)	X	X	X	X	X	X	X
MAST	X					X	X

DAST	X					X	X
Neuropsych battery (currently used at WRIISC CA)	x					X	X
Executive function (DKEFS)	X					X	X
Pure Tone Audiometry	X					X	X
MRI Scan	X					X	X
Epworth Sleepiness Scale (ESS)	X					X	X
Pittsburgh Sleep Quality Index	X					X	X
MAPI	X					X	X
Treatment Log	X	X	X	X	X		
Brief Pain Inventory (BPI) interference score	X	X	X	X	X	X	X

Patients are tested for "improvement" after the 20th session (on the primary outcome measure) and if improvement is shown, they will be enrolled for a 6 month follow-up. Units of 5-10 sessions will normally be delivered over one week's time. As is the case with other somatic treatments such as electroconvulsive therapy, some consideration of scheduling flexibility must be made to accommodate holidays and other events. These units of 5-10 sessions can be delivered over a minimum of 5 calendar days and should be delivered within 12 calendar days. Thus, the entire acute treatment phase (initial 20 sessions) would normally take in 2 weeks (depending on scheduling constraints). At the end of every fifth session, study staff will enter progress notes for each participant in CPRS. *Follow-up Phase:* After the acute treatment phase ends, patients showing post treatment improvement will enter a 6 month follow-up period. Follow-up visits will occur approximately every six months during the follow-up phase. If a participant does not remit at the end of 20 sessions of treatment or drops out during treatment, the participant will be considered a treatment failure for the purpose of the primary analyses. Participants will be paid $200 for the entire rTMS treatment visit (including baseline assessment and MRI) and $100 for the six month follow up MRI visit.

E. Intervention Regimen: *Selection of rTMS Stimulation Parameters:* We will be using the parameters that are currently FDA approved for Depression (George et al, 2010) and are being used in CSP-556 Depression clinical trial (PI: Yesavage) and rTMS for pain in GW1 Veterans (PI: Ashford) at the VA Palo Alto. The proposed parameters are the most likely, based on current knowledge, to be potentially effective in the VA population. The specifics are: Location: DLPFC; Power: 120% of motor threshold as separately determined for each patient prior to treatment/sham sessions; Pulse frequency: 10 Hz; Length of each pulse train: 5 seconds; Time between pulse trains: 10 seconds; Length of treatment: 20 minutes; Total 4000 pulses per session, 5 days/week, 20 session (completed in 2 weeks depending on scheduling constraints). Location & Intensity**:** rTMS analgesic studies have ranged from dose of 80% MT to 120% MT depending on the site selected for treatment stimulation. Older studies used lower intensity stimulation because of safety concerns at the time which have now relaxed with greater experience. In several recent studies, 120% MT is sufficient to stimulate the prefrontal cortex in all subjects under age 70, even those with prefrontal atrophy (Nahas et al., 2004). It is both tolerable, and safe. (Sham (Control) treatment: This system, or something quite similar, has been used in the OPT-TMS depression clinical trial (e.g. CSP556) and several other smaller studies and the blind has been maintained. Sham (Control) treatment will be accomplished by using the Cool-B65-A/P coil that functions both as an active (A) and placebo (P) coil. It has a symmetrical mechanical design and no labeling on the coil indicates the active or placebo side. Consequently it is not possible for the operator to see or hear which side is used. Additionally, for each treatment session, whether sham or active, each patient shall wear scalp electrodes through which, in the case of sham treatments, a low-voltage, low electric current (2 – 20ma at no more than 100V) will be passed in order to provide cutaneous stimulation that mimics the sensation of actual rTMS. At the same time, the Sham Noise Generator is used to hide the click noise produced by the rTMS. That is, when a magnetic stimulation pulse is fired, white noise is sent to the ears of the patient. This sham (white) noise will hide the click noise from the participant (active or placebo)).

F. Neuroimaging Acquisition: (WRIISC CAneuroimaging laboratory is currently involved in two funded neuroimaging studies and is responsible for analysis of all clinical MRIs done weekly at WRIISC CA. We have dedicated staff, servers, and (Veteran Affairs Hospital) resources that are currently utilized for (equipment and data) quality (checking). The following MRI sequences will be run on all patients (pre and post treatment and 6 month follow-up) using standard 8 channel head coil and current sequences at PAVA: a high-resolution structural MRI, DTI and Functional MRI resting state. All sequences are regularly conducted under WRIISC CA clinical and research time at the GE 3T MRI scanner and take less than one hour).

V. Data Management: (see Human Subjects).

VI. Biostatistical considerations:

A. Primary Analyses, Effect Size and Potential Clinical Impact

There is a general consensus that rTMS has both a clinically significant analgesic effect where the moderate effect size is Cohen's d of about 0.65. Since only one study has been conducted in TBI patient, we established our sample size based on Moser et al., (2002) where in a sample of 19 middle-aged to older adults (with refractory depression) there was a significant improvement on Trail Making Test (TMT: our main outcome measure) in the rTMS versus sham group (Cohen's d = 0.8). We doubled the sample size and propose to enroll 40 Veterans diagnosed with mild and moderate TBI (age range 20-65) during 1.5 years in this study. (Attrition Plan: As stated above we are conservatively estimating a probable 20% attrition rate over the course of this study. Therefore, we will recruit, screen, and randomize an additional 12 participants to ensure that we have a sufficient sample size to adequately perform our proposed analyses (final sample size after accounting for attrition, n = 52).). The primary endpoint is a pre-post rTMS change in age-adjusted executive function measures and the effect of rTMS will be tested in a logistic regression model with TBI status treated as a categorical variable. We are confident that our effect size will provide an adequate measure of rTMS efficacy to treat executive function deficits in mild and moderate TBI. In addition to testing for statistical significance, we will convey practical significance by reporting treatment effect sizes and their confidence intervals (for all analysis).

B. Secondary Hypotheses: To test the secondary hypotheses of sustained improvement in executive function improvement, we can use logistic regression to analyze the length of significant improvement in executive function performance. We will also estimate the impact of initial failures during the treatment phase on achieving improvement at the critical 20th session time point. (As shown in Table 3, we are collecting measures of depression and other variables at screening/baseline, post-treatment and follow-up so we can look at improvement in these measures). This analysis will have a sample size defined by the number of patients achieving the study's primary endpoint and covariates observed up to the date of the 20th session will be included as predictors. Logistic regression will also be used to test for potential moderators of Response in this pilot study. Age, severity of time since injury symptoms at baseline, type of comorbidity (PTSD, depression substance abuse, sleep, fatigue or any combinations of these), (TBI type), duration of illness (and prior or current treatment effects e.g., medication or cognitive rehabilitation) may affect or "moderate" treatment response. Assuming a sample size of 40, a stable logistic regression can be performed with at least 2 but not more than 4 degrees of freedom for the model (based on 5-10 events per d.f.). (As this is a pilot study we are limited by the number of participants in order to address secondary effects on cognition that may be statistically meaningful). The purpose of these analyses will be to detect apparent reversals of effect, or major quantitative interactions, in order to describe the uniformity or variation of effect across major subgroups appropriately. *Neuroimaging Data Analysis:* (All image processing methods described below are already established at WRIISC CA. 1) T1-weighted MRI: Volumetric segmentation on structural scans will be performed with the Freesurfer image analysis suite generating Estimated Total Intracranial Volume (eTIV) used for normalization. The technical details of these procedures are described in prior publications (Segonne et al., 2004). 2) *DTI:* The fiber tracts from the whole brain tractography will be classified into 20 fiber structures as defined in the standard white-matter tractography atlas (Wakana et al., 2007) using a modified form of the reference ROI approach (Zhang et al., 2008; see Fig 2). 3) *Resting State fMRI Analysis:* Image preprocessing will be carried out using tools from FMRIB's Software Library (FSL; version 4.1) (Smith et al., 2004). Following preprocessing and alignment using Jenkinson et al., (2002) methods, a dual regression technique will be applied (Damoiseaux et al., 2012) to perform voxelwise between group (treatment & sham) comparisons of resting state connectivity at each time point. Networks of interest that may serve as biomarkers for capturing improvement in EF after rTMS treatment will be Default Mode, Left and Right Executive and Salience Networks (see Fig 3). Additionally, we will also obtain pre- and post- treatment network differences and include them in a regression model along with treatment/sham group, age, TIV and other significant moderating variables (e.g., PTSD) to predict improvement in EF (pre- post- treatment change in the EF outcome measures).) *(BDNF Plasma Levels:* Both blood and saliva samples will be obtained and frozen. Plasma concentrations of BNDF will be measured using enzyme-linked immunosorbent assay (ELISA). It is expected that EF improvement will correlate with BDNF plasma levels.)

VII. Data Safety Monitoring Plan: See Human Subjects

VIII. Safety and Risks: See Human Subjects