Long Term efficacy of rTMS in Managing MTBI-related Headache

NCT03314584

December 6, 2023

Human Protocol (Version 1.32)

General Information

***Please enter the full title of your study::**

Long Term Efficacy of rTMS in Managing MTBI-Related Headache

***Please enter the Study Number you would like to use to reference the study:**

Long Term Efficacy TBI
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

Add departments

and Specify Research Location:

Is Primary?	Department Name
◉	**VASDHS** - VASDHS

Assign key study personnel(KSP) access to the study

***Please add a Principal Investigator for the study:**

Leung, Albert Y., MD

3.1 If applicable, please select the Research Staff personnel

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***Please add a Study Contact**

Kennedy, Michelle, BA
Leung, Albert Y., MD
Lopez, Caleb, BS

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

VASDHS IRB
Human Subjects Protocol
v20190121

Section 1 - Preliminaries

Principal Investigator:

Albert Y. Leung, MD

Protocol Title:

Long Term Efficacy of rTMS in Managing MTBI-Related Headache

IRB Protocol Number:

H170053

Protocol Nickname:

Long Term Efficacy TBI

Form Template Version:

v20150115

Date Prepared:

12/06/2023

Please be advised that this protocol application form has changed as a result of the 2018 Common Rule. There are new questions and sections, and you may be required to provide additional information to previous sections.

1a) Is this study considered human research?

- (•) Yes
- ( ) No
- ( ) I don't know

1b) Please select:

- ( ) This is an application for a NEW human subject research protocol
- (•) This is a revision of an existing protocol

Was this study initially approved prior to January 21, 2019?

(•) Yes ( ) No

Were you instructed to convert to the 2018 Common Rule Requirements?

(•) Yes ( ) No

Section 2 - Research Subjects

2a) What is the total planned number of VA-consented subjects?

Include the total number of subjects who will prospectively agree to participate in the study (e.g., documented consent, oral consent, or other).

200

2b) What is the total number of VA subjects who WILL NOT be consented?

Include the total number of subjects that will be included without consent (e.g., chart review). *Note: Data about people are still considered "human subjects" by the IRB, so even if you do not intend to contact the patients whose charts you will review, you still should enter the number of charts as your "planned subjects."*

0

Section 2.1 Consented Subject Groups

2.1) For each of the subject categories listed below, indicate whether or not these subject groups will participate in the study:

2.1a) Children under the age of 18
Note: If neonates or children will be involved in this study, certification by the Medical Center Director will be required. Only minimal risk research may be performed with children. Only non-invasive monitoring and/or prospective observational and retrospective record review studies that are minimal risk can be conducted in VA involving neonates.

( ) Yes (•) No

2.1b) Pregnant women

( ) Yes (•) No

2.1c) Individuals with cognitive/decisional impairment

○ Yes ◉ No

2.1d) Non-English-speaking individuals

○ Yes ◉ No

2.1e) Prisoners of War (explicitly targeting this group)

○ Yes ◉ No

2.1f) Non-Veterans (Note: Justification for inclusion of non-Veterans will be required)

◉ Yes ○ No

2.1g) Incarcerated individuals (Note: VA CRADO approval will be required)

○ Yes ◉ No

2.1h) VA employees - including VA paid, IPA, or WOC (Note: Union review and authorization may be required)

○ Yes ◉ No

2.1i) Students of the institution (e.g., resident trainees) or of the investigator

○ Yes ◉ No

2.1j) Patients with cancer (or high cancer risk) [explicitly targeting this group]

○ Yes ◉ No

Section 3 - Study Features (these items default to "No" for convenience)

3) This section consists of several Yes/No questions addressing protocol characteristics. Click on *Save and Continue*.

Section 3.1 Protocol Basics

Select all that apply

3.1a) The research **intends to change** the participant.

◉ Yes ○ No

3.1b) **Interactions** with living participants to collect data or specimens with no intent to change them.

○ Yes ◉ No

3.1c) This is a study that **never** has any **subject contact and does not collect subject identifiers**

○ Yes ◉ No

3.1d) This is a **chart review** study involving retrospective or prospective medical records.

○ Yes ◉ No

3.1e) This is a **multi-site** study occurring in-part or in-full at other locations.

○ Yes ◉ No

3.1f) There is an **international** component to this research. *International research includes sending or receiving human derived data or specimens (identifiable, limited data set, coded, or deidentified) to or from an international source. International research does not include studies in which VA is only one of multiple participating sites where the overall study-wide PI is not a VA investigator.*

○ Yes ◉ No

3.1g) This study includes **off-station activity** (not including VA-leased space or CBOC clinics) conducted under VASDHS IRB approval. *Note: this does not include research conducted by a collaborator at their home institution under their institutional approval.*

(•) Yes ( ) No

3.1h) VA subjects will **participate** in part or in full **at other locations** (not including VA-leased space or clinics) under VASDHS IRB approval. *Note: if this study involves remote participation of subjects, please indicate "no" and describe their remote participation in section 9 of the application. This question is intended to understand whether participants must physically go to a non-VA location to participate in this VA research study.*

(•) Yes ( ) No

Section 3.2 Specimen Use and Data Repository

Indicate whether or not each of the following applies to this protocol

3.2a) Involves specimens that are left over from pathological or diagnostic testing (**non-research specimens**)

( ) Yes (•) No

3.2b) Involves **specimens collected for research** purposes **only**

( ) Yes (•) No

3.2c) This study includes **specimen banking** (specimens are retained for use outside of the purposes of this protocol)

( ) Yes (•) No

3.2d) The study involves **DNA** genotyping or other **genetic analysis**

( ) Yes (•) No

3.2e) Biological **specimens/material** will be sent outside of the VA.

( ) Yes (•) No

3.2f) A **data repository** is maintained (data are retained after completion of the protocol for other uses, IMPORTANT: see **?** before checking "yes")

( ) Yes (•) No

3.2g) **Data will be shared outside** of the VA (identifiable, coded, limited data set, or deidentified)

( ) Yes (•) No

Section 3.3 Treatment and Clinical Trials

Indicate whether or not each of the following applies to this protocol

3.3a) Includes a **treatment** component (a research treatment)

(•) Yes ( ) No

3.3b) Study is a **clinical trial.** *Note: A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.*

(•) Yes ( ) No

3.3c) Has a data safety monitoring board (**DSMB)** or data safety monitoring committee.

(•) Yes ( ) No

3.3d) Has a **data safety monitoring plan** (but not a DSMB) (this is not the data security plan, it is a safety plan).

○ Yes ◉ No

Section 3.4 Drugs and Devices

Indicate whether or not each of the following applies to this protocol

3.4a) **Drugs** that require **FDA** action such as an Investigational New Drug (IND) approval or exemption or 510 (k) approval.

○ Yes ◉ No

3.4b) Other drugs, supplement, etc. that **do not require FDA** action for inclusion in the study.

○ Yes ◉ No

3.4c) Medical **devices requiring FDA** IDE approval or waiver

◉ Yes ○ No

3.4d) **Other** medical **devices**

○ Yes ◉ No

Section 3.5 Risk and Hazards

Indicate whether or not each of the following applies to this protocol

3.5a) Study places subjects at **greater than minimal risk** (do not include risks that are due to standard care)

◉ Yes ○ No

3.5b) Human subjects are exposed to **radioisotopes** (do not include standard care).

○ Yes ◉ No

3.5c) Subjects have other **radiation exposure** (e.g., x-rays) (do not include standard clinical use).

○ Yes ◉ No

3.5d) Target population has psychiatric diagnosis, behavioral complaint, or chronic pain.

○ Yes ◉ No

Section 3.6 Clinical Facilities and Standard Care

Indicate whether or not each of the following applies to this protocol

3.6a) Study **uses VA clinical services** (e.g., adds required tests run in the VA lab for study purposes; research procedures concurrent with clinical care)

○ Yes ◉ No

3.6b) Includes procedures or drugs that will be considered **part of standard care.**

○ Yes ◉ No

3.6c) Involves **lab tests done for research** purposes.

○ Yes ◉ No

Section 3.7 Subject Expenses and Compensation

Indicate whether or not each of the following applies to this protocol

3.7a) There may be expense or added **costs to the subject** or the subject's insurance.

○ Yes ◉ No

3.7b) This is a **qualifying cancer treatment trial** and subjects may be billed for study drugs or procedures.

○ Yes ◉ No

3.7c) This is a cancer treatment trial but **subjects will not be billed** for study drugs or procedures.

○ Yes ◉ No

3.7d) Subjects will be **compensated** (either in cash or other means such as a gift certificate).

◉ Yes ○ No

Section 3.8 Subject Activities

Indicate whether or not each of the following applies to this protocol

3.8a) Involves **surveys or questionnaires** completed by subjects

◉ Yes ○ No

3.8b) Includes the use of **recruitment materials** such as flyers, advertisements, or letters

◉ Yes ○ No

3.8c) Involves facial **photographs** or audio or video **recordings** of **patients**

○ Yes ◉ No

Section 3.9 Sponsors and Collaboration

Indicate whether or not each of the following applies to this protocol

3.9a) This research is a funded research project **(commercial (industry) sponsor, NIH, VA, other).**

◉ Yes ○ No

3.9b) Other **commercial (industry) non-financial support** is provided (e.g., drugs or supplies).

○ Yes ◉ No

3.9d) The protocol has **Department of Defense** involvement (e.g., subjects or funding).

○ Yes ◉ No

3.9c) The PI or other study staff member has a financial interest or other **real or potential conflict** related to this study.

○ Yes ◉ No

3.9e) This study involves **collaborative** research activities (research conducted at other institutions under the authorities or approvals of the other institution/s). *Note: this may include other VA and/or non-VA institutions, but does not include off-site VA research.*

◉ Yes ○ No

Section 4 - Estimated Duration

4) What is the estimated duration of the entire study? (From IRB approval to IRB closure)

6 years

Section 5 - Lay Language Summary

5) Provide a summary or synopsis of the proposed study using non-technical language (not more than 1 paragraph)

Persistent headache is one of the most common debilitating symptoms in military personnel suffering from mild traumatic brain injury (MTBI). This study aims to assess the long-term effect of repetitive transcranial magnetic stimulation (rTMS) in managing MTBI related headaches for up to 2-3 months by comparing the treatment effect of active-rTMS to sham-rTMS.

Section 6 - Specific Aims

6) Provide a statement of specific aims and hypotheses that serve as the basis for this protocol. Emphasize those aspects that justify the use of human subjects.

1) Compare the long term treatment effect of active rTMS (Group A) to sham LMC rTMS (Group B) in reducing the intensity, frequency and duration of MTBI-HA and the overall analgesic usage;

Hypothesis #1: Active rTMS at LMC provides significantly more reduction in headache intensity, duration and frequency of exacerbation than sham rTMS;

2) Compare the long term treatment effects of Group A to Groups B in improving quality of life, mood and functions in patients with MTBI-HA;

Hypothesis #2: Active rTMS at LMC provides significantly more improvement in quality of life, mood and functions than sham LMC stimulations;

Coinciding with the specific aims, the proposal also consists of the following exploratory aims:

1) Explore the treatment effect on resting state supraspinal functional connectivity in the pain related network;

2) Explore moderators' effect of injury mechanisms (blast and non-blast) and the headache severity on the treatment .

Section 7 - Background and Significance

7) Provide a succinct discussion of relevant background information to justify performing the proposed study.

Background

Headache is one of the most common debilitating chronic pain conditions in either active or retired military personnel with MTBI. This high prevalence of persistent chronic headache is often associated with neuropsychological dysfunction in mood, attention, and memory, which casts a profound negative impact on patients' quality of life and increases stress in their caregivers. Unfortunately, as witnessed by the investigators in their clinical practices, conventional pharmacological treatments for MTB related headache (MTBI-HA) has not been shown to be effective and drugs such as narcotics contain many long-term untoward psychosomatic and abusive side effects [13; 50; 60]. This calls for an urgent need in developing alternate and innovative long-term headache management strategies for this rapidly increasing patient population.

Our group was the first in the VA system to adopt brain magnetic resonance imaging (MRI) neuronavigation guided repetitive transcranial magnetic stimulation (rTMS) as a non-invasive treatment option for chronic pain including MTBI-HA in 2010. Our prospective follow-up survey indicated over 150 patients with MTBI-HA treated with rTMS demonstrated over 50% reduction in headache intensity with correlated reduction (>50%) in the frequency and duration of debilitating headache exacerbation. Close to 90% of these initial treatment responsive patients are currently on a maintenance treatment protocol, which continues to demonstrate sustainable headache prevention and relief benefit. This ongoing clinical observation supports the feasibility of using rTMS for long-term headache management in patients with MTBI-HA. ***Further support for adopting this innovative therapy for MTBI-HA comes from our recently completed randomized sham controlled study indicating an initial week long course (3 sessions) of rTMS at the left motor cortex (LMC) can alleviate MTB related headache symptoms and reduce the exacerbation pattern for up to one month without significant side effects. 80% of the patients received the real treatment demonstrated at least 50% headache reduction in comparison to only 20% of the patients in the sham group [43]****. For long-term management, published case series show subsequent maintenance treatment sessions can be feasibly applied at a much lesser frequency than the initial sessions of rTMS with sustainable headache relief benefit [41; 81]. Coinciding with other published treatment protocols related to traumatic brain injury and pain [32; 55], this initial clinical evidence provides compelling support for the current proposal aiming to assess the effect of a longer duration of rTMS protocol in managing MTBI-HA for up to 10 weeks after the initiation of the treatment.* Given existing treatment options for MTBI-HA are limited, validating such a non-pharmacological and non-invasive treatment option will significantly enhance the capability of the VA healthcare system in caring for this rapidly increasing patient population.

Pathophysiology of MTBI

In assessing the underlying pathophysiology of MTBI related morbidities, although gross structural lesions are usually not detected by conventional anatomical brain neuroimaging techniques such as MRI or computer tomography, studies with diffusion tensor imaging (DTI) suggest that MTBI patients suffer from diffuse axonal injury in the major cortical white matter tracts including corpus callosum, anterior corona radiata, corticospinal tract, and internal capsules, which are crucial for intracortical connectivity. Th ese abnormal findings as reflected by the diminished fractional anisotropy index found in the frontal cortices and often directly correlated with deficit in fine motor skill, attention, mood and memory identified with neuropsychological and motor functional assessments [5; 59]. In the area of neurophysiological assessments, MTBI patients appear to suffer from long lasting elevation of resting motor threshold, suggesting a deficiency in cortical excitability and conductivity in brain areas associated with pain modulation/adaptation in this patient population [71]. In addition, these structural and electrophysiological abnormalities found in MTBI population also correlated with findings in a blood perfusion study, which demonstrated MTBI patients presented with hypoperfusion in the basal ganglion, a key relay center between the cortical areas (particularly the prefrontal cortical area and parietal cortices) and the limbic system, suggesting a dissociative state between the affective (hyperactive) and modulatory (hypoactive) aspects of suprapsinal activities [46]. ***Our studies with functional magnetic resonance imaging (fMRI) further confirmed a diminished state of supraspinal prefrontal cortical modulatory***

functional connectivity to other pain related supraspinal regions in patients with persistent MTBI-HA in comparison to age and gender matched healthy controls in both resting and evoked pain states [44]. Therefore rectifying this dissociative state and enhancing supraspinal modulatory functional connectivity by means of non-invasive brain stimulation can be the key for addressing MTBI related symptoms.

Central Pain Processing and Modulation

Based on previous studies, the supraspinal pain processing network is known to involve thalamus (TH) and pons, which relate sensory afferent signs to other supraspinal regions including: 1) sensory discriminatory regions such as the primary and secondary somatosensory cortices (SSC1 and SSC2), and the inferior parietal lobe (IPL); 2) affective regions such as the anterior cingulate cortex (ACC) and the insula (IN); and 3) modulatory regions involving various regions of the prefrontal cortices (PFCs) [54]. Decreases of medial prefrontal cortical activities and other motor cortical functions are known to be associated with central hyperalgesia [68]. As pain perception and relief relies heavily on the balance between the affective and modulatory/adaptive functions of the pain network, a disruption in the intra-dynamic of the network such as diminished modulatory/adaptive function can often lead to the development of central pain states with associated neurological symptoms (chronic headache), and neuropsychological dysfunction (attention deficit and depression) [8; 72]. Consequentially, one of the feasible ways to correct the imbalance is to actively stimulate the modulatory supraspinal regions that are known to exhibit endogenous analgesic and mood enhancing benefits.

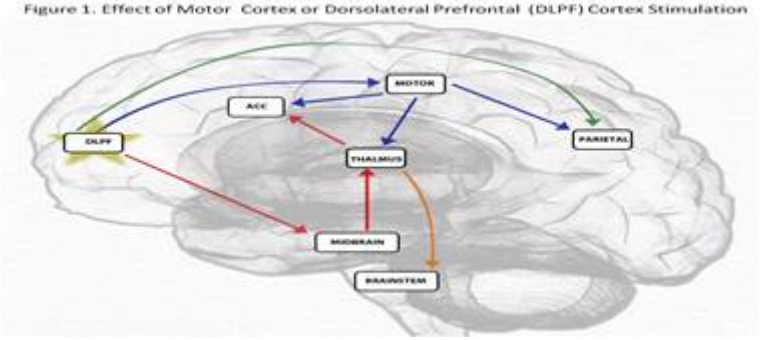
Transcranial Magnetic Stimulation (TMS) for Pain and Behavioral Functions

Recognizing these structural, electrophysiological and neuropsychological abnormalities associated with MTBI provides an opportunity to formulate potential treatment strategies for this patient population. TMS non-invasively stimulates the brain by utilizing electromagnetic principles to produce small focal electrical currents in the cortex [74; 75]. The device usually consists of an insulated electric coil, which with the passing of electrical current generates a dynamic magnetic field through the scalp and skull, and into the first few millimeters of the cortex without attenuation. A figure-of-eight coil is commonly used because it gives a precise localization. Depolarization of corticospinal tracts with TMS occurs at about the junction of the grey and white matter [14]. Studies in animal demonstrate that TMS can alter neural plasticity by affecting the amount of beta-adrenergic receptor in rat cortex consistent with the response to all clinically effective antidepressants and electroconvulsive shock [3; 18]. Other studies concur that TMS has the ability to influence neuron-transmitters, receptors and associated second messengers systems, which are important in pain regulation [29; 33]. TMS also has the ability to increase gene activity in neural and supportive elements which are important for nerve repair/regeneration in neurofunctional degenerative conditions such as MTBI [21].

While both dorsolateral prefrontal cortex (DLPFC) and motor cortex (MC) high frequency (> 1Hz) rTMS can result in an analgesic benefit, their relative mechanisms appear to be different. With stimulations at the motor cortex, a strong focal activation was observed in thalamus, insula, cingulate-orbitofrontal junction and periaqueduct grey (PAG) area in the brainstem, suggesting that a direct top-down activation of descending pain control system mediating via a motor-thalamus and/or motor-brainstem functional linkage [22; 63]. On the other hand, rTMS at the DLPFC exerts a “top-down” inhibitory effect along the descending midbrain-thalamic-cingulate pathway through the descending fibers from the prefrontal cortex [48; 49]. In addition, while administering naloxone will block the analgesic effect of high frequency (10hz) motor cortex rTMS, it has no effect on the analgesic effect of left DLPFC stimulation suggesting that the analgesic effect mediated via the DLPFC stimulation may not be directly related to endogenous opioid release [9]. However, these two regions appear to be highly interactive with the left

DLPFC stimulation found to potentiate the excitability of the MC [61]. Given that tonic pain reduces motor intracortical excitability, stimulating the motor cortex provides the **most direct** means in restoring motor cortical excitability and its pain modulatory functions. (See figure below: different arrow colors represent different interconnected pathways) [7]. In the area of clinical evidence, ***although evidence supporting rTMS at the DLPFC for mood enhancement in depression is strong (level A evidence), its support for treating central neuropathic pain states or headache is not as robust as rTMS at the MC as one recent study has found DLPFC stimulation ineffective for poststroke central pain [10]. On the other hand, a consortium of European experts has found level A evidence of "definite efficacy" of high frequency (> 1Hz) rTMS of the primary MC for neuropathic pain states [37].***

Figure 1. Effect of Motor Cortex or Dorsolateral Prefrontal (DLPF) Cortex Stimulation



Aside from enhancing inter-cortical connectivity, rTMS can also correct brain pre-existing structural abnormalities and improve functional deficit. rTMS is also known to increase white matter FA in cortical and subcortical regions in patients suffering from stroke and depression respectively with correlated functional and behavioral improvement [56; 62]. ***A previous meta-analysis study conducted by the investigators demonstrated the analgesic benefit of rTMS at the MC appeared to have a neuroanatomical hierarchy suggesting pain originating from the more centrally located neuroanatomical structure responds more favorably than peripherally originated neuropathic pain states [42]. Increasing evidence suggests that MTBI result in central neurological injury as in post-stroke central pain, and thus supporting the notion that persistent MTBI-HA represents a central neuropathic pain state [19; 39; 44]. Thus, the use of rTMS at the MC as a useful and safe way of neuromodulation in managing the associated headache (neuropathic pain) and neuropsychological deficits. In regards to treatment protocols, although various treatment protocols have been reported for pain and headaches, a recently published guideline for neuropathic pain and other published studies related to traumatic brain injury suggests a 10 consecutive weekday treatment regimen at 10/20 Hz as the initial treatment protocol. In addition, outcomes of the intervention should be observed several weeks after the treatments [32]. With the MTBI-HA relief benefit observed one month after a short course (3 sessions) of rTMS at the left MC [43], the proposed study adopting this longer duration of treatment sessions will likely result in more robust long term benefits in headache management.***

Safety of rTMS

rTMS is currently FDA approved for treating major depression and single pulse TMS is approved for treating migraine headaches. This treatment technology has an excellent safety track record when used under the safety guideline established in 1998 [74]. ***A recent study demonstrated that unilateral rTMS as well as bilateral combined rTMS revealed no detrimental effects on cognition in comparison to the sham group 3 months after the treatment [2].*** On the other hand, rTMS is found to have mild beneficial cognitive effects [24]. In lack of any major breakthrough in establishing other effective long-term treatment regimen for MTBI-HA and co-morbidities, this safety track record and potential benefits associated with rTMS supports the feasibility of the proposed study in a rapidly growing patient population with debilitating symptoms.

PTSD and MTBI

Headache, MTBI and Post-traumatic Stress Disorder (PTSD) can be co-morbid conditions [51; 78]. Therefore, the potential benefits of rTMS in relieving PTSD related symptoms have been assessed in the investigators' previous studies related to rTMS and MTBI-HA. While in both studies (one published, one in preparation)[43]*, the investigators found patients with MTBI-HA on average consists of a slightly elevated score in the Clinician Administered PTSD Scale (CAPS), the majority of the individual scores and their overall average score did not meet the clinical diagnostic criteria of PTSD. In addition rTMS did not appear to have a significant impact in either improving or worsening their overall CAPS scores. Therefore, while patients will be screened for PTSD, the current proposed study will primarily focus on the stated specific aims. However, screening the study cohort's baseline (pre-treatment) PTSD severity will allow the investigators to conduct analyses if necessary with built-in covariates should the baseline CAPS scores are significantly different (although not expected) between the two proposed study groups.*

Preliminary Data

Our group has conducted several prior studies to support the feasibility of the current proposal. The results of these studies are discussed as follows:

1) rTMS for neuropathic pain and MTBI-HA

In a collaborative meta-analysis study [39] from six major multinational TMS research centers with pooled individual data (n=149) from 5 published clinical trials, we were able to reveal the overall treatment effect of rTMS in neuropathic pain states. The result of the analysis strongly suggests that the analgesic efficacy of multiple sessions of rTMS is more superior to a single session of rTMS as the overall treatment effect for the multiple session study is 20.4 % significantly (P=0.003) better than the overall effect of the single treatment session studies. The analysis also demonstrates the effect of rTMS on neuropathic pain consists of a differential "top-down" pattern based on the neuroanatomical origins of the neuropathic pain pathophysiology with centrally originated pain states such as post-stroke central pain syndrome as the top responders **(see below for excerpted study result figures) to motor cortex rTMS.** Like the post-stroke central pain patients, MTBI patients are known to demonstrate central diffuse neuronal injury, which makes them the ideal candidates for the treatment.

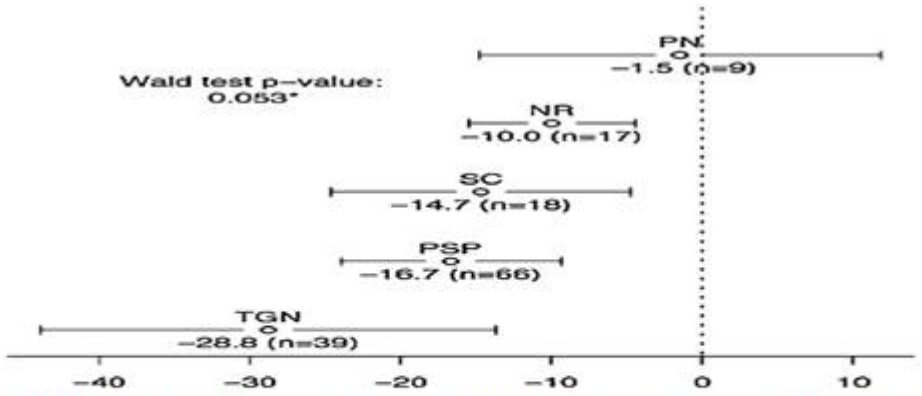


Figure 3. Diagnosis and treatment effect. Mean difference (95% confidence interval) in percent of pain visual analog scale (VAS) score change.*P value is from Wald test for the interaction effect of diagnosis and treatment on the percent decrease in VAS score. This P value increases to 0.140 when we exclude the Khedr study. NR, nerve root; PN, peripheral nerve; PSP, post-stroke supraspinal related pain; TGN, trigeminal nerve or ganglion.

2) rTMS at the LMC in reducing MTBI-HA

In our recently published study, MTBI-HA subjects were randomized to receive three sessions of either real (N=12) or sham (N=12) rTMS at the left motor cortex with brain MRI neuronavigation guidance. Subjects received the real rTMS demonstrated a significantly higher degree of headache relief up to one month in the comparison to the sham group (see below for excerpted figures 3a and 3b from Appendix #6a) [44]. This observed headache relief efficacy with a relatively short duration of treatment sessions warrants further studies assessing the long–term benefit of rTMS in MTBI-HA management with a more robust and longer duration of treatment sessions.

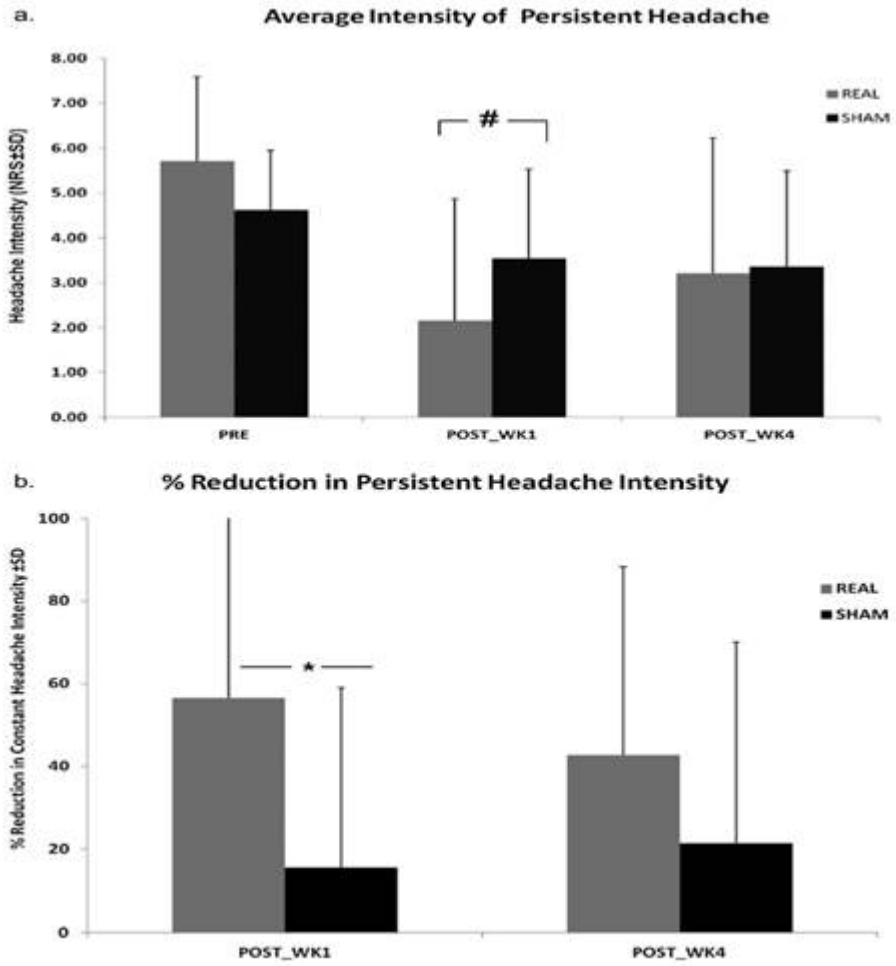


Figure 3. Change of persistent headache. a. Intensity of persistent headache in numerical rating scale (NRS), # $p = 0.06$. b. Percentage of reduction in persistent headache,*$p < 0.05$. Post_WK1: posttreatment one week; Post_WK4: posttreatment four weeks.

3) Prospective Case Series demonstrating the feasibility of rTMS in long-term management of MTBI-HA

Our internal prospective follow-up survey in over 150 patients and recently published case series supports the feasibility of using rTMS as a long-term therapeutic tool for MTBI-HA and migraine headache management [41; 81]. A well powered sample size and controlled study with a longer duration of treatment is warranted.

4) Supraspinal Functional deficit in patients with MTI-HA

Our published studies with functional magnetic resonance imaging (fMRI) suggest that patients with persistent MTBI-HA have significant

compromised medial prefrontal modulatory response to heat pain stimuli and their resting state medial prefrontal cortical connectivities to other pain related regions are diminished in comparison to age and gender matched healthy controls **(See excerpted study figures 3&4 from appendix #6b) [44].** Although a previous study suggested blast-related traumatic brain injury (TBI) appeared to have a unique effect on brain function associated with cognitive inhibitory tasks that could be distinguished from TBI resulting from non-blast (blunt or motor vehicle injury) related TBI [17], our preliminary assessment with experimental heat pain stimulation found no significant difference in supraspinal modulatory response to experiment heat pain between blast (n=7) and non-blast Veterans (N=7) (Leung et al., unpublished data). When turning our attention to assess the headache severity related supraspinal pain modulatory functions, we found Veterans with **Mild (**£I 4 on a 0-10 NRS, numerical pain rating scale) intensity of headache appeared to have higher level of left medial prefrontal cortical function in comparison to their counterparts with **Moderate-to-Severe (≥5 on 0-10 NRS)** head ache intensity in their response to heat pain stimulation under functional magnetic resonance imaging (fMRI). Therefore further mechanistic exploration is required to understand the potential impact of injury mechanisms and headache severities on the treatment outcome.

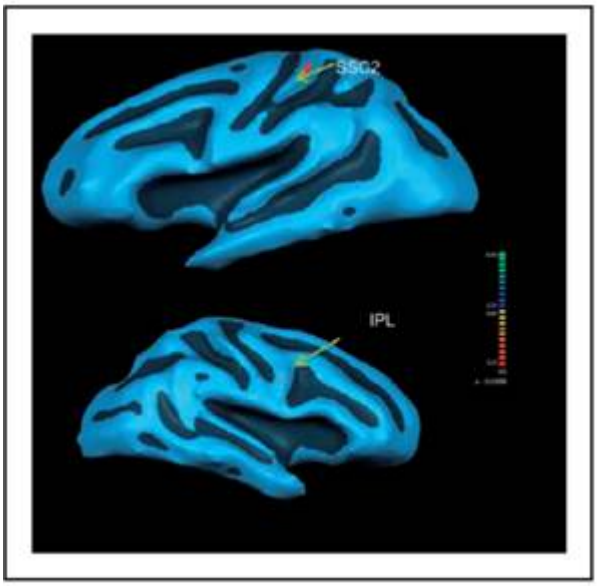


Figure 3. Resting state functional connectivity difference with the left medial prefrontal cortex (seeded region) of the Healthy Controls ($N = 15$) demonstrating more significant ($P < 0.01$) functional connectivity to the left secondary somatosensory cortex (SSC2) and right inferior parietal lobe (IPL) than patients with mild traumatic brain injury ($N = 15$).

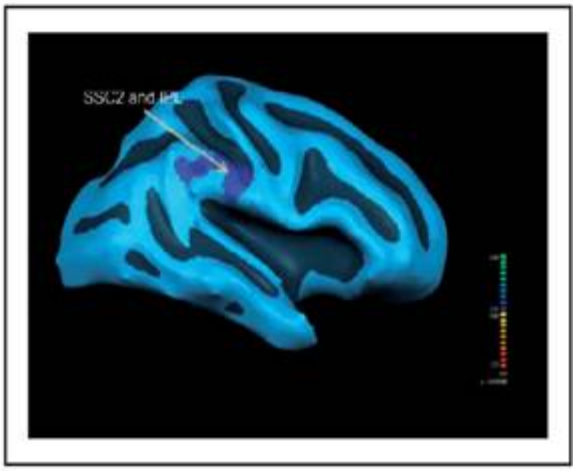


Figure 4. Resting state functional connectivity difference with the right anterior cingulate cortex (seeded region) of the healthy controls ($N = 15$) demonstrating less significant ($P < 0.01$) functional connectivities to the right secondary somatosensory cortex (SSC2) and inferior parietal lobe (IPL) than patients with mild traumatic brain injury ($N = 15$).

Section 9 - Design and Methods

9) Describe the research design and the procedures to be used to accomplish the specific aims of the project. Provide a precise description of the planned data collection (include what systems or databases will be used/accessed to gather data), analysis and interpretation. For chart review studies, include the timeframe of collection. Address sample size, inclusion of women and minorities. Define in clear terms exactly what will be done to the human subjects.

Research Design:

A total of 200 will be consented and 128 (64 per group, accounted for 36% dropout rate) patients will be randomized to be stratified based on their injury mechanisms (blast, non-blast) and headache severities (mild, moderate, severe) and enrolled over 6 years from VASDHS, and Naval Medical Center San Diego (MNCSD). Patients meeting study enrollment criteria will be randomized into one of the two study groups (A&B) based on their mechanisms of injury, gender, severity of headache, and past failed therapies for their headache. The overall study duration for each subject is about 14 weeks developed into three phases according to the following schedule:

1) PRE-TREATMENT PHASE (weeks 1-2) consists of Visit 1 (Screening Visit) and Visit 2 (Pre-treatment Assessments);
2) TREAMENT PHASE (week 3-4) consists of Visits 3-12 (Neuronagvigation guided rTMS consisting of 10 weekday treatments at >24 and < 72 hours apart, weekends excluded, maximum 5 weeks for treatment completion) rTMS will take place in Building 23 Room 105 at the VASDHS; and

3) POST-TREATMENT PHASE (week 5-14) consists of two initial weekly visits (Visits 13&14) and two additional biweekly visits (Visits 15&16) and one monthly visit (Visit 17).

Brain anatomical and functional MRI will be performed within 72 hours after Visits 2 and 13. Subjects will be required to fill out headache diary between assessment visits. Headache assessments along with quality of life, mood and functions assessments will be carried out at Visits 1,2, and 13--17. This frequency of treatment and duration of follow-up is in line with recently published rTMS articles related to TBI, headache and pain, and also in accordance with the 3-month post treatment initiation follow-up guideline /recommendation [32; 55; 80].

A) Headache assessment (specific aim #1, see Appendix 6b for assessment samples)

Due to the persistent and debilitating nature of MTBI-HA, two areas of headache characteristics: **1) Persistent Daily Headache**; and 2) **Debilitating Headache Exacerbation** will be especially assessed during the study in addition to more conventional headache assessments. Patients will be provided with a daily headache diary, which they will fill out every evening during the study between-visit periods (B1-B6). In the diary, they will report if they have a persistent (non-stop, 24/7) headache over the last 24 hours and rate the average intensity of the headache on a 0-10 Numerical Rating Scale (NRS). In addition, they will be asked to report the duration and intensity of any debilitating headache exacerbations, which completely incapacitate their daily functions.

For persistent headache, the intensity of the headache from the diary will be averaged (sum of headache NRS scores/number of days) as between-visit persistent headache severity assessment. Should the headache becomes sporadic after the study rTMS interventions, the subjects will then record the total number hours of headaches over the previous 24 hours and the average intensity of the headache, they will still record the duration and intensity of any debilitating headaches. The occurrence of lingering persistent daily headaches and average intensity of daily headaches will be recorded [38; 43].

For debilitating headache exacerbation, a composite score will be generated by multiplying the average duration (hours/episode) of the headache exacerbation by the average frequency (episodes per day) and the average intensity (NRS) of the headache exacerbation [38; 45] .

Aside from assessing the daily intensity and exacerbation pattern of MTBI-HA, additional assessments for the impact of headaches on the patients' quality of life will include:

1) the **Headache Impact Test (HIT-6)** which will assess the impact of headaches on the subjects' ability to function on the job, at school, at home and in social situations [66; 79];

2) **Neurobehavioral Symptom Inventory (NSI) assessment which** will assess the pattern of headaches and other co-morbid neurological symptoms in Visits 2, 13, 14, 15, 16 & 17 [31; 60]. As a fail-safe assessment for any missing data, subjects will also be asked to rate the average intensity of headache in Visits 2, 13, 14, 15, 16 and 17 for the prior between-visit durations on a 0-100 Mechanical Visual Analogue Scale (M-VAS) [64].

B) Neuropsychological Assessments (Specific Aim #2, see Appendix 6c for assessment samples)

Attention, memory, executive functioning and depression are commonly disrupted following TBI and for some, these impairments persist as part of a post concussive syndrome [52]. There is evidence to suggest that rTMS has resulted in benefits in these same cognitive domains [11]. The tests in the assessment battery were selected with several factors in mind: (a) validity and reliability; (b) relevance to the literature and prior experience with these tests in previous studies of rTMS; (c) limiting the length of the battery to reduce fatigue and facilitate compliance; (d) targeting measurement of neurocognitive functions commonly found to be impaired in patients with TBI. Details regarding the following measures are provided in Appendix 6c.

I). Cognition: (a) Attention: Conner's Continuous Performance Test (CPT II) [4; 58] and added Eye-Tracker assessment. (b) Memory: Hopkins Verbal Learning Test[16; 36; 73]; (c) Executive Functioning: Trail Making Test A and B; Stroop Test ;

II). Mood: Hamilton Rating Scale for Depression (HRSD) [1; 6; 65];

III). Quality of Life: SF-36**;**

IV). PTSD (only at Visit 2): Clinician-Administered PTSD Scale (CAPS); and

IV). Global Pain: Brief Pain Inventory (BPI)

The duration of all neuropsychological/behavioral tests is estimated to be less than 2 hours 45 minutes. The duration of the assessment appears to be reasonable and non-excessive for the patients based on the investigators' previous experience. However, if the subjects are unable to complete all the assessments in one setting, they will be asked to return in the following day to complete the assessment.

C) Other study associated assessments consist of:

1) Weekly Phone Assessment: After the post-treatment one-week assessment, the study coordinator will conduct weekly phone contacts with the subjects for pain and side effect assessments until the completion of the study. The study coordinator will also trouble shoot any potential issues that may lead to unnecessary subject dropout with the assistance of the PI;

2) **Side Effect Assessment:** During each study related visit (after Visit 2) and weekly phone assessment, side effect assessment will be conducted to monitor any study related complication. Patient will be asked to report any

potential neurological side effect such as soreness at the side of the treatment, dizziness, or increase of pain related to the treatment. Investigators will determine whether these side effects are study or non-study related and report to the Institutional Human Subject Protection Committee, VA Research and Development Committee and the study Data Safety Monitoring Board according to the protocol; and

3) **Concomitant Medication:** Any medication that a subject uses during the study is considered concomitant medication. This includes prescription and non-prescription treatment such as contraceptives, vitamins, topical preparations, herbal preparations, and non-pharmacological therapies. Concomitant medication information (please see Human Subject for allowable and prohibited concomitant medications during the study) will be collected for all subjects during the screening, treatment, between visits (recorded in the Daily Headache Log) and subsequent post treatment visits. Information regarding subjects' previous failed treatments will also be collected at the screening visit. Subjects will be instructed not to alter medication regimens during the study without consultation with the investigators.

D) Functional imaging

Resting state functional imaging of the brain will be obtained after (within 72 hours) Visits 2 and 13. To minimize medication related interference, patients will be asked not to take any headache related rescue medications 24 hours prior to the scanning. Head movement during scanning will be minimized by instructing the subjects to hold their head still during the scanning, applying padding between the subjects' head and the head coil, and having subjects wear a cervical collar to minimize both lateral and axial head movements [40; 69]. 5-minute resting fMRI data will be collected via a 1.5T GE scanner with T2*- weighted EPI-sequence (TE=30 ms, TR=2.0s, a=90°, TH=4mm, 32 slices, FOV=220x220 mm^2, MA=64x64.

Evoked Heat pain state fMRI will be conducted according to a well established protocol[79-81] (See Appendices 3B&3C). During the scan, an intermittent thermal heat pain stimulation will be delivered via a thermode controlled by a computer at the left calf area in 15 second pulse rates for about 10 minutes. The equipment used is called a quantitative sensory threshold (QST) and has been used in several pervious studies.

To be consistent with the stimulation site in the study, the location for the evoked heat pain measurement was marked at the medial aspect of the left calf between the 6^{th} and 7^{th} marking of an elastic band which consisted of a total of 13 increments, extending from the medial malleolus to the medial tibial plateau. This method of peripheral sensory testing has been well established in literature and has been used extensively in pain-related studies [74-78]. The subjects are then asked to rate the intensity of HP on a M-VAS.

E) Study intervention

Prior to study intervention (within 72 hours of Visit 2), brain anatomical scans will be obtained with rapid gradient-echo (MP RAGE) sampling (176 slices T1, 256x256 and 1cm slice thickness) in GE 3.0 MRI scanner. The images will then be processed by ANT Visor2-XT software for the neuronavigation guided rTMS treatments according to the following protocol:

I). Preparation: The patients will be asked to sit in a comfortable chair and relax as much as possible. Electromyography (EMG) recordings from the contralateral abductor digit minimi (ADM) muscle will be acquired with silver-silver chloride surface electrodes, using a muscle belly-tendon set-up, with a 3cm diameter ground electrode placed at the wrist. Manufacturer pre-installed software will be used to collect signal with a recording time window of 200ms. TMS will be performed with a figure-of-eight coil connected to MagPro B65 (Alpine BioMed, Fountain Valley, CA). Before beginning a rTMS session, subjects will be asked to sit in the study intervention chair with the rTMS coil positioned on their head, keeping their head as still as possible for 3.5 minutes. This is to acclimate the patients to the study intervention set-up prior to initiating the intervention.

II). TMS Neuronavigation System

All patients' brain anatomical MRI will be obtained and examed by Dr. Roland Lee, Chief of Neuroradiology. The acquired scans will then be processed by the ANT Visor 2-XT Software. During TMS Neuronavigation, stereotaxic data for the localization of the TMS stimulation site are recorded and will allow the investigators to visualize the TMS coli and focus the magnetic flux onto the target region. The three fiducial points (nasion, left and right perauricular), treatment location will be marked onto the patients' cortical image so that the location of each treatment and distance between the center for the coil and target region will remain the same for each treatment session. This approach will account for the variability of location between subjects and treatments, which may arise without the neuronavigation guidance.

III). Determination of resting motor threshold

This assessment will be conducted at the first (Visit 3) and the last (Visit 12) treatment session. A constant suprathreshold stimulus intensity will be applied via a figure-of-eight coil, which will be moved under the guidance of TMS Neuronavigation over the left motor cortex (Brodmann Area 4). Once the optimal location is visually identified, a single pulse TMS will be delivered to that location starting at the suprathreshold intensity and decreasing in steps of 2 % of the stimulator output. The resting motor threshold (RMT) will be defined as the minimal intensity required to elicit motor evoked potentials of 50 V peak to peak amplitude in five out of 10 consecutive trials [30]. The location of the cortex used for the establishment of the RMT will be marked on the neuronavigational software and used for subsequent treatments. The distance between the center of the probe and the target site will be recorded as well.

IV). Active/Sham-rTMS at left MC

Active or sham rTMS will be delivered via the MagVenture Cool-B65 Active /Placebo coil which performs as a coil with both active (A) and placebo (P) functions. This is an ideal coil for double-blinded clinical studies requiring a very high number of stimuli. It consists of a built-in orientation software controlled by the randomization code , which determines which side of the coil should be placed towards the subject. The coil symmetrical design with no indication of active vs. placebo sides makes it ideal for double-blinded studies. This coil with the projection of live neuronavigation guidance images and noise generator addresses several pertinent blinding parameters related to rTMS clinical trials by providing: 1) the auditory click of coil discharge; 2) the visual stimulation including the coil location and orientation; 3) the tactile sensation of coil tapping or scalp muscle activation; and 4) no direct brain stimulation when the placebo coil is faced towards the targeted brain region. The treatment site for the left MC will be the same as the site where the RMT is determined. The stimulation target will be marked on cortical surface using the ANT Neuronavigation System, which is compatible with the Cool B65 A/P coil. The marked location will be used for all subsequent treatments. Active-rTMS consists of 20 trains with each train containing 100 pulses delivered at 10 Hz and 80% RMT stimulation intensity over the area as determined above. A total of 2,000 pulses will be delivered at each area over 3 to 4 minutes. This treatment protocol is within the treatment safety guideline recommended by the FDA and the PI has been using this protocol for over six years with good clinical outcome and minimal side effects [74].

VI). Process of randomization and treatment double blinding

The un-blinded study biostatistician, Dr. Golshan, will create a list of patient identification numbers with randomized treatment assignments (A = Active/Real, B = Sham) using the SPSS software prior to the start of the study subject recruitment. Blocked randomization will be used with random block size of 3 or 6. Separate lists (up to 12) of replacement patient identification numbers will also be created so that replacement patients are assigned the same treatment as patients they are replacing. Patients will be randomized to study treatment groups in a 1:1 ratio. Dr. Golshan will be contacted by the study coordinator with subjects' unique master ID number (sequential number, independent from any protected health information or any other identification source) and their descriptive information. After a subject signs the study consent, the study coordinator will be provided with that subject's randomization code. A minimization random assignment procedure will be used to match subjects on four variables: 1) mechanisms of injury; 2) gender; 3) severity of headache, and 4) past failed therapies for their headache. The minimization random assignment procedure aims to obtain equal numbers of subjects at the different levels of each matching variable. In contrast to stratified randomization, which aims for equal numbers of subjects in each treatment for every possible combination of the interested variables, the minimization method restricts its aim to equalizing treatment numbers at the different levels of each variable taken separately [20; 77]. Essential for this study, the procedure allows sequential assignment of subjects. This method has been shown to be superior to both simple and

stratified randomization in producing a balance for separate prognostic variables, particularly when the number of strata is large in comparison with the number of subjects. In addition to violations of inclusion and exclusion criteria, reasons for randomization failure include major protocol deviation, lost to follow-up, voluntary withdrawal, and study termination will be communicated with Dr. Golshan. The randomization code will be input into the TMS software in guiding the orientation of the Cool B65 A/P coil for each subject based on a built-in gravity sensor mechanism. This method of double blinding with the use of Cool B65 A/P coil as recommended in a recent guideline for rTMS in pain/headache related studies [32] will blind both the subjects and the investigators to the study treatments.

E) Blinding Strategy and Assessment

In addition to the double blinding A/P coil, several blinding strategies will be applied to minimize biases in the study: 1) All subjects are allowed to visualize the TMS coil over the cortical treatment sites on a projected screen and hear the clicking noise during either active or sham rTMS; 2) Standard instruction before and after each rTMS treatment will be given to each subject to minimize instructional related study biases; 3) The procedure for determining the RMT will be identical for each subject. To ensure adequate blinding throughout the study, all subjects will be surveyed whether they receive active-rTMS (Groups A) vs. sham-rTMS (Group B) at Visits 5, 8 and 14; and 4) To minimize investigators' bias, the study coordinator responsible for assessment will go through extensive training by the study PI prior to enrollment of any subjects on both the protocol and administration of assessments. The inter-rater reliability (an intra-class correlation coefficient of $\geq$ 0.90) between the study coordinator and the gold standard will be established by the PI. This reliability will be monitored every six months by study statistician, Dr. Golshan. Both the study coordinator and the investigators will be blinded to the treatment given to the subject. The randomization list will be provided by the study biostatistician. In addition, all data collected will be organized and sent directly to the biostatistician for analysis without going through the PI or any other investigators.

F) Weekly Phone Assessment

After the TREATMENT PHASE, the study coordinator will conduct weekly phone contacts with the subjects to ensure their compliance with filling out the headache diary and to assess any side effect until the completion of the study. The study coordinator will also trouble shoot any potential issues that may lead to unnecessary subject dropout with the assistance of the PI.

G) Side Effect Assessment

During each study related visit and weekly phone assessments, side effect assessments will be conducted to monitor any study related complication. Patient will be asked to report any potential neurological side effect related to the study treatment. Investigators will determine whether these side effects are study or non-study related and report the findings to the Institutional Human Subject Protection Committee, VA Research and Development Committee

and the study Data Safety Monitoring Board according to the protocol. If necessary, severe adverse events such as death , suicide, or other life-threatening events or issues will be reported immediately to the HRPP for expedited reporting.

Data Management, Analysis and Power Calculations:

Missing data values will be minimized by intensive training of the staff involved in the study. Missing data will be examined to assess randomness and the pattern of missing data according to the procedure recommended by Little and Rubin [47]. The investigators will test whether the dropouts are random or systematic by comparing the dropouts with the study completers on the baseline data. An absence of significant differences would support the random nature of dropouts.

Initially, descriptive statistics and exploratory graphing such as frequencies, means, standard deviations, box and whisker plots, stem and leaf diagrams, and scatter plots will be used to assess the normality of the data in terms of the presence of skew and/or outliers. The continuous outcome data will be transformed if necessary by using an appropriate transformation such as the log transform for skewed long tailed data. Similarly, potential covariates will also be summarized with descriptive statistics and graphs to determine the most appropriate way to treat these variables and to decide if a continuous, categorical, or an interval representation is the most appropriate approach.

Data acquired in this project will be managed and analyzed by the study statistician, Dr. Golshan. Customized database system will be developed for this project to ensure the highest possible data reliability by the study biostatistician. The system will include but is not restricted to: (i) patient demographic input and query; (ii) patient recruitment, scheduling and protocol tracking; (iii) data storage, compilation, selection, and summary transfer to various statistical and graphical sub-systems; (iv) administrative document and report management and, (v) data backup and archival control. Data entry programs will include item prompts, skip patterns, range checks, and logical validity routines. Standard data security protocol will be used for this project. These include, but are not limited to: assigning a unique ID number for each subject, storing confidential information in an encrypted form, using VA secure server, limiting accessibility of data to authorized Center personnel. An electronic archive of all data is kept offsite to insure against loss by fire, theft, etc. All statistical transfer routines are inherently secure via their operating platform and they contain no patient names or personal data.

For hypotheses 1 and 2, where multiple analyses are conducted, correction for family-wise Type I error rates will be made using the Westfall-Young randomization maxTprocedure, which adjusts p-values for significance while taking into account the correlation of the outcomes [76]. In this way, the study can control for an overall family-wise error rate of .05 while achieving more power than Bonferroni adjustments. Using this method of power analysis, the investigators estimated a sample size of 128 (64 per group, accounted for a 20% dropout rate) provides the study with 85% power

to detect a medium effect size (RMASS program provided by Hedeker) [25; 26]. Medium effect sizes were used based on the results included in the above sections. Medium effect size is defined as a between-group difference increasing linearly from 0 at baseline to .5 SD units at the last time point. The minimum power estimation is based on sample size calculation for 10% and 20% attrition, correlations of 0.2, 0.5, and 0.8 between the repeated measures, and for medium and large effect sizes. Data will be analyzed using SPSS version 23, all analyses will be two-tailed, where applicable with = .05.

Hypothesis #1: Active rTMS at LMC provides significantly more reduction in headache intensity, duration and frequency of exacerbation than sham rTMS.

Independent Variables: Treatment Groups with two levels (Groups A & B), Visits up to 8 (See below). Dependent Variables: Primary outcome: Average daily headache assessments (B1, B2, B3, B4, B5, B6); Secondary outcome: Debilitating Headache Composite Score (B1, B2, B3, B4, B5, B6); M-VAS Scores of headache (Visits 2, 7, 12, 13, 14, 15, 16 17); HTL-6 and NSI (Visits 2,13,14,15, 16, 17); headache rescue medication usage (Visits 2,13, 14, 15,16, 17). Note, not all variables are collected at all visits.

Statistical Analysis:

Data will be analyzed using mixed effects model [12; 27; 35]. This approach provides more information and therefore, more power compared to cross-sectional analyses, which focus on the analysis of one summary index, or more traditional analytic approaches such as a change score, end-point or repeated measures analysis of variance. In this approach, the repeated measures over time for each individual subject form a trajectory that can be described by a relatively simple model with a few parameters, such as intercept (baseline value) and slope (rate of change). With repeated measures, repeated observations within subjects are potentially correlated for any impact on the resulting tests of significance [34]. When this within subject correlation is properly incorporated, the repeated measures analysis takes full advantage of all information obtained from each subject, thereby greatly increasing the statistical power over methods that compare treatments cross-sectionally [23]. This approach can model for the differential patterns over the repeated assessments, instead of the totals at one point. As a result, this analytical approach increases the reliability of the measurement of response (since the slope combines repeated measures, which cancel much of the error of measurement), and will increase the protection against the major effects of missing data. In addition, the influence of missing data is reduced since it maximizes the number of subjects by allowing the inclusion of subjects with missing data, dropouts or those who are terminated early in the study without relying on data imputation procedures. The investigators will use pattern-mixture models to assess if there is any bias due to drop out or missing data. These will result in

increased power to detect effects and precision for the estimation of the effect sizes without requiring increased sample size, and provide the study with a uniform method of data analysis for all hypotheses that include multiple measurements from the same subjects. The mixed effects model method provides an estimate of the individual variability around the population trend, the variability of the individual intercepts (baseline values) and slopes (changes across time), and the correlation between them. A fully saturated treatment by time model will be utilized for inference. Co-variance structure will be chosen based on Akaikes Information Criterion (AIC). This allows for any group level effects to be incorporated into the model. Denominator degrees of freedom will be calculated using the Kenward-Roger small sample correction. Analyses will be conducted within and across nested levels of the study design; this will involve within-subject analyses (comparison of occasions of measurement nested within an individual), as well as between-subject analyses (comparison of two groups). In addition, any treatment group comparison can be adjusted for subject-specific characteristics and adjustments for changes in these characteristics over the course of the study, and incorporated into the single-subject analyses. Based on investigators' experience with previously completed studies, we expect a dropout rate of 10 to 20% throughout the study. All analyses will be two-tailed, where applicable, with = .05. Correction for family-wise Type I error rates will be made using the Westfall-Young randomization maxTprocedure, which adjusts p-values for significance while taking into account the correlation of the outcomes [70]. In this way we can control for an overall family-wise error rate of .05 while achieving more power than Bonferroni adjustments.

Hypothesis #2: Active rTMS at LMC provides significantly more improvement in quality of life, mood and functions than sham LMC stimulations.

Independent Variables: Treatment Groups with two levels (Groups A & B), Visits with 8 levels: pre-treatment (Visit 2), treatment (Visits 7 &12), and Post-treatment (Visits 13,14, 15, 16, 17).

Dependent Variables: Attention (CPT II), Memory (Hopkins Verbal Learning Test) Execute function (Trail Making Test A and B, and Stroop Test), Hamilton Depression Scale, SF-36 and BPI.

Statistical Analysis: Data will be analyzed similar to hypothesis 1 and we estimated to have a minimum power of 85% for these analyses using similar method described above.

Exploratory aims:

1) Explore the treatment effect on resting state supraspinal functional connectivity;

2) Explore moderators' effect of injury mechanisms (blast and non-blast) and the headache severity on the treatment outcomes.

Effect of treatment on the resting state supraspinal functional connectivity will be explored by using Self-organizing Group Level Independent Component Analysis (SogICA)[15; 28]. Primary focus will be placed on the mediopreffrontal cortices (MPFCs) and the anterior cingulate cortex (ACC) regions, which were found to have altered functional connectivity in the MTBI patients in comparison to healthy controls in a recently published study conducted by the investigators [44]. These regions will serve as the primary seeded regions for subsequent pre- and post-treatment between-group ANCOVA resting state functional connectivity analyses. Additional levels of exploratory analyses will also include baseline between-group assessments with and without factoring in the mechanisms of injury and headache severities. For exploratory aim #2, the Injury mechanism (blast vs. non-blast) will be explored by adding it as independent variables to the mixed model. The effect of initial headache severity (Visit 2) will be explored by adding this baseline outcome to the mixed model as a fixed covariate.

Children and Women

No children will be recruited for this study. VA requires a waiver for a research on children and currently VASDHS does not offer a pediatric service. Female subjects who meet the study inclusion and exclusion criteria will be recruited. Female Subjects at childbearing age will be required to have a urine pregnancy test prior to the enrollment.

Follow Up Appointments in response to COVID-19:

In response to COVID-19, we are requesting that follow up visits be conducted via telephone, Doximity, and/or email. Questionnaires (Headache Impact Test, Neurobehavioral Symptom Inventory, Brief Pain Inventory, SF-36, and Modified Fatigue Impact Scale) will be emailed to subjects to view and a phone or Doximity call will be conducted where subjects can verbally respond to the questionnaires emailed and the Hamilton Rating Scale for Depression and Hopkins Verbal Learning Test will be administered. This will be applicable for subjects currently in the follow up phase and for use only during the COVID-19 response.

Protocol Changes in Response to COVID-19

In response to the COVID-19 pandemic, we are proposing changes in study design with increased safety measures based on the 12-step model listed in "Guidelines for TMS/tES Clinical Services and Research through the COVID-19 Pandemic" by Ehktiari et al. to reestablish research and open enrollment while mitigating potential risks associated with the virus. The changes to the protocol will

consist of conducting baseline and follow up assessment visits over phone or video call. Some assessments will be removed due to the inability to conduct them over phone/video call. Consenting and screening will also be conducted over the phone/video call. In addition, stringent safety and sanitization measures will be implemented to reduce risk that include limiting staff presence, PPE for subjects and staff, COVID-19 screening, and increased and frequent sanitization of equipment.

STUDY DESIGN - COVID-19

The original study design was conducted according to the following schedule where all visits were conducted On-site:

Visit 1: Consent and Screening Visit;

Visit 2: Pre-treatment Assessments and MRI Scan;

Visits 3-12: Study Treatments;

Visit 13: Post-treatment 1-week assessment and MRI Scan;

Visit 14: Post-treatment 2-week assessment;

Visit 15: Post-treatment 4-week assessment;

Visit 16: Post-treatment 8-week assessment;

Visit 17: Post-treatment 12 -week assessment

To reduce physical interaction and exposure risk, a new study timeline will convert all visits that do not necessitate an on-site visit (i.e. consenting, screening, and assessments) to remote telehealth visit. In addition, visits 2 and 13 will be broken up to 2 visits in which assessments will conducted remotely and the MRI conducted on site. These on-site visits will not be implemented until written approval from the ACOS/R&D that on-site visits may be resumed. The visits will be revised as the following with visits either conducted through telehealth (TH) or onsite (OS):

1: Consent/Screen - TH;

2a: Pre-treatment (TX) Assessments - TH;

2b: Pre-TX MRI - OS;

3-12: Induction Treatments - OS;

13a: Post-TX 1-week assessment - TH;

13b: Post-TX MRI - OS;

14: Post-TX 2-week assessment - TH;

15: Post-TX 4-week assessment - TH;

16: Post-TX 8-week assessment - TH;

17: Post-TX 12-week assessment - TH;

The following table summarizes the visits, location of each visit, timeline, and procedures to be conducted at each visit:

Visit	Visit Name	Location	Timeline	Procedures
1	Consent /Screen	Telehealth	Day 0	Consent/HIPAA Form Screen for eligibility
2a	Pre-TX Assessments	Telehealth	Within 7 days of consent	Assessments and Questionnaires
2b	Pre-TX MRI	On-Site	Within 1-2 days of V2a	Anatomical, DTI, Resting and HP fMRI Physical exam for screening
3-12	Induction Treatments	On-Site	First treatment to begin 7-10 days of V2b	TMS Treatments (>24 and <72 hours apart)
13a	Post-TX 1 Week Assessments	Telehealth	Within 6-8 days of V11	Assessments and Questionnaires
13b	Post-TX MRI	On-Site	Within 6-8 days of V11	Anatomical, DTI, Resting and HP fMRI
14	Post-TX 2 Week Assessments	Telehealth	Within 28-31 days of V11	Assessments and Questionnaires
15	Post-TX 4 Week Assessments	Telehealth	Within 28-31 days of V11	Assessments and Questionnaires

16	Post-TX 8 Week Assessments	Telehealth	Within 56-62 days of V11	Assessments and Questionnaires
17	Post-TX 12 Week Assessments	Telehealth	Within 84-93 days of V11	Assessments and Questionnaires

Table 1: Summary of Study Design in Response to COVID-19

TELEHEALTH VISITS

All telehealth visits will be conducted through video call through Doximity or VA Video Connect. However, phone calls will be available as back up if there are issues with connectivity or other technical issues preventing video. Video calls will allow the study team to better monitor subjects and create a more personal visit.

Consent/Screening – Visit 1

Consent and screening will take place remotely in which a member of the study team will go over the study details, eligibility, and answer any questions or concerns. Subjects will be given a copy of the consent/HIPAA forms prior to the scheduled visit through MyHealtheVet or mail. Once the consent form/HIPAA has been reviewed and the subject agrees to participate, the subject will be asked to sign the forms (either handwritten or electronically) and return the forms to the study team through either MyHealtheVet or FAX. Subjects will also be screened for the study and COVID-19 over the video call and a physical exam will be conducted by the PI during the first on-site visit (2b). If a subject indicates they have had symptoms of COVID-19, they will be advised to come into the hospital for testing. A negative test (or confirmation that they are no longer positive) will be required before enrollment.

Once a subject is enrolled, an additional phone call will be conducted prior to their baseline assessments to go over the various platforms (Doximity, MyHealtheVet, and VA Video Connect) that will be used for the telehealth visits.

Assessment Based Visits – Pre-treatment assessments (V2a), Post-TX 1-week (V13a), Post-TX 2-week (V14), Post-TX 4-week (V15), Post-TX 8-week (V16) and Post-TX 12 week (V17)

Pre and post-treatment assessments will be conducted over video call, and questionnaires to be completed by subjects will be provided prior to each visit through MyHealtheVet or mailed to the subjects. Subjects will be given the choice to either: 1) complete questionnaires within 24hours of their video appointment and

return them through MyHealtheVet or FAX; or 2) complete them during the video call where subjects will provide their verbal responses and the study coordinator will document the response. The following assessment will have changes on administration:

1. Mechanical Visual Analogue Scale (MVAS) of Headaches, Muscle, and Joint Pain: subjects will rate their pain on the 0-100 MVAS scale at all On-site visits

The following assessments will not be conducted as they require in-person administration:

1. Stroop Test
2. Eye Tracking Assessment
3. Conner's Performance Test II
4. Trail Making Test

These assessments are part of the secondary hypothesis, measuring attention and executive functioning. Though these functions will not be measured, the primary aim of this study is to assess headache and quality of life and assessments related to the primary aim will still be administered.

All other assessments listed in the protocol will be administered with no changes, other than being conducted remotely. Subjects will continue to keep a daily log of their headaches and medication usage throughout the course of the study which will be collected by either sending it through MyHealtheVet or through FAX.

The following table summarizes the assessments/questionnaires administered:

Visit		**2a**	**2b**	**3-12**	**13a**	**13b**	**14**	**15**	**16**	**17**
Location		**TH**	**OS**	**OS**	**TH**	**OS**	**TH**	**TH**	**TH**	**TH**
Brief Pain Inventory-Short Form (BPI)	Self-administered	x			x		x		x	
Neurobehavioral Symptoms Inventory (NSI)	Self-administered	x			x		x		x	
		x			x		x		x	

Headache Impact Test (HIT-6)	Self-administered					
Short Form Health Survey-36	Self-administered	x	x	x	x	
Hopkins Verbal Learning Test (HVLT)	Study Coordinator	x	x	x	x	
Hamilton Rating Scale for Depression (HRSD)	Study Coordinator	x	x	x	x	
Clinician-Administered PTSD Scale (CAPS-5)	Study Coordinator	x	x	x	x	
Modified Fatigue Impact Scale	Self-administered	x	x	x	x	
MVAS – Sliding Scale	Study Coordinator	x	x	x	x	x

TH: Telehealth; OS: On-site

Table 2: Summary of Assessments in Response to COVID-19

ONSITE VISITS (ONCE WRITTEN APPROVAL FROM ACOS /R&D FOR RESUMING ON-SITE VISITS IS PROVIDED)

MRI scans (2b and 13b) and treatment-based visits (3-12) will be conducted onsite at the UCSD fMRI Center and at VA San Diego Building 23, respectively, with increased safety measures.

Section 9.4 Devices

9.4) For each research device, state the status of the device, the PI's determination as to whether the device is a significant or non-significant risk device, and provide justification for this determination. A copy of determinations from the FDA should be attached. - Also, for investigational devices describe how and by whom the device will be received, stored, secured and dispensed.

Device: TMS Magpro Magventure, previously approved through engineering department for research studies H130281, H160047

rTMS is currently FDA approved for treating major depression and single pulse TMS is approved for treating migraine headaches. This treatment technology has an excellent safety track record when used under the safety guideline established in 1998 [74]. A recent study demonstrated that unilateral rTMS as well as bilateral combined rTMS revealed no detrimental effects on cognition in comparison to the sham group 3 months after the treatment [2]. On the other hand, rTMS is found to have mild beneficial cognitive effects [24]. In lack of any major breakthrough in establishing other effective long-term treatment regimen for MTBI-HA and co-morbidities, this safety track record and potential benefits associated with rTMS supports the feasibility of the proposed study in a rapidly growing patient population with debilitating symptoms.

The PI believes that this device does not meet the definition for a significant risk device (SR) and therefore falls into the non-significant risk (NSR) device classification under the current FDA guidelines:

According to the FDA, under 21 CFR 812.3(m), an SR device means an investigational device that:

• Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
• Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious
risk to the health, safety, or welfare of a subject;
• Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise
preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of
a subject; or
• Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Therefore, the PI has determined an abbreviated IDE designation is applicable due to the fact that this device is a NSR that has been approved by the FDA, however for the study it will be used in an off-label manner. (http://www.fda.gov/oc/ohrt/irbs/devrisk.pdf)

Similar devices have also been studied and the results concerning device safety have been published:

1. Anand S, Hotson J. Transcranial magnetic stimulation: Neurophysiological applications and safety. Brain and Cognition. 2002;50:366-386.
2. Rossini PM, Rossi S. Transcranial magnetic stimulation: diagnostic, therapeutic, and research potential. Neurology. 2007;68:484-488.
3. Wassermann EM, Lisanby S. Therapeutic application of repetitive transcranial magnetic stimulation: a review. Clin Neurophysiol. 2001;112:1367-1377.

Further information on Transcranial magnetic stimulation:

The principle of inductive brain stimulation with eddy currents has been noted since the 20th century. The first successful TMS study was performed in 1985 by Anthony Barker and his colleagues in Sheffield, England.[4] Its earliest application demonstrated conduction of nerve impulses from the motor cortex to the spinal cord, stimulating muscle contractions in the hand. As compared to the previous method of transcranial stimulation proposed by Merton and Morton in 1980[5] in which direct electrical current was applied to the scalp, the use of magnets greatly reduced the discomfort of the procedure, and allowed mapping of the cerebral cortex and its connections.

4. Barker, AT; Jalinous, R; Freeston, IL (1985). "Non-Invasive Magnetic Stimulation of Human Motor Cortex". The Lancet 325 (8437): 1106–1107. doi:10.1016/S0140-6736(85)92413-4. PMID 2860322.
5. Merton, P. A.; Morton, H. B. (1980). "Stimulation of the cerebral cortex in the intact human subject". Nature 285
(5762): 227. doi:10.1038/285227a0. PMID 7374773.

FDA DOCUMENTS
MagPro rTMS: K091940 & K061645
MEDOC TSA II NeuroSensory Analyzer: k010981 & TSA-II_Brochure (FDA Approval)
Request for NSR justification & abbreviated IDE designation
MagPro rTMS: This device study is one that does not meet the definition for an SR device study and therefore falls into the NSR classification under the current FDA

The device has been used by the PI in 5-6 approved studies, the latest one being protocol #H160047.

Section 9.8 Questionnaires & Surveys

9.8) Provide the name and a reference for questionnaires/surveys that are standard or identify them here and attach a copy of the questionnaire/survey. ***Questionnaires or surveys that are not clinical standard references must be uploaded. Reference the help link for additional information related to surveys administered to VA personnel and approved platforms for web-based surveys.***

Questionnaires & Surveys (copies attached):

1.Numerical Pain Rating Scale (NPRS): scale that ranges from no pain to worst possible pain.

2.Headache Log: Daily log to report if they have a persistent (non-stop, 24/7) headache over the last 24 hours and rate the average intensity of the headache on a 0-10 Numerical Rating Scale (NRS). In addition, they will be asked to report the duration and intensity of any debilitating headache exacerbations, which completely incapacitate their daily functions.

3.Neurobehavioral Symptoms Inventory (NSI): A self-report on the severity of each symptom is measured using a 5-item scale. It asks the subjects to indicate the extent to which each symptom has disturbed them.

4.Headache Impact Test (HIT-6): Measures how impact headaches affect the individual's ability to function in different domains.

5.Short Form Health Survey-36: A patient-reported survey of patient health. It is a measure of health status and quality of life in regards to eight main areas: vitality, physical functioning, bodily pain, health perceptions, physical, emotional, and social role functioning and mental health.

6.Clinician-Administered PTSD Scale (CAPS-5): A 30-item structured interview that can be used to diagnose PTSD and associated symptoms.

7.Conner's Continuous Performance Test (CPT II): A widely used test of sustained attention using a computer program. It provides a detailed picture of response time, impulsivity, and attentiveness.

8.Hopkins Verbal Learning Test: Hopkins Verbal Learning Test: This is a verbal list learning measure with multiple equivalent forms to minimize practice effects in repeat testing. It provides information about learning acquisition as well as short and long delayed recall. It has been used successfully in previous trials of rTMS.

9.Trail Making Test A and B: This is a widely used test of executive functioning. It consists of an attention/processing speed condition (connecting numbers in order quickly) followed by a more complex sequencing task (alternating between numbers and letters).

10.Stroop Test: Participants must inhibit a pre-potent response to provide the required response on this test of inhibition.

11. Hamilton Rating Scale for Depression (HRSD: This scale is a well-established questionnaire which consists of 21 questions and rates the severity of symptoms observed in depression such as low mood, insomnia, agitation, anxiety and weight loss. The scale is frequently used in TBI related studies for assessing the severity of depression.

12. Brief Pain Inventory: Assesses the intensity of physical pain and the levels of interference using a numerical rating scale (1 to 10).

13. Eye-Tracker Assessment: assesses eye movement during a test to learn more about attention in this population.

Section 9.9 Data Safety Monitoring Board or Plan

9.9) Provide a Data Safety Monitoring Plan (DSMP) or the details of a Data Safety Monitoring Board; if a

written plan is available, attach a copy of the plan to the submission form.

The DSMB will review all unanticipated problems involving risk to study subjects, serious adverse events, and all subject deaths associated with the protocol, and provide an unbiased written report of the event within 10 calendar days. The DSMB will provide an independent evaluation of adverse events and unanticipated problems involving risk to subjects to the Human Subject Protection Committee. The DSMB will comment on the outcomes, adverse events, and relationship of the events to the protocol. The DSMB will
indicate whether they concur with the details of the report provided by the PI. The DSMB promptly reports discrepancies or problems to the Committee. They have the authority to stop a research study in progress,remove individual volunteers from a study, and take whatever steps will be necessary to protect the safety and well being of research subjects until the IRB can assess the report. The members of the DSMB for this proposal will comprise of a pain specialist, a clinical psychologist and a biostatistician who will be independent of the investigative team and possess sufficient educational and professional experience to serve as the subjects' advocate. The members of DSMB also have no apparent conflicts of interest.

The DSMB members include:

Carter Jones, M.D., Ph.D. (pain specialist)
Dr. Jones is an Assistant Professor of Anesthesiology at UC San Diego, School of Medicine, with sub-specialty training in pain management.

William Perry, Ph.D. (psychologist)
Dr. Perry is a Professor of Psychiatry at UC San Diego, School of Medicine. He is the Associate Director of the Neuropsychiatry and Behavioral Medicine Service at the UCSD-Medical Center. He also serves as the Chief Supervising psychologist at UCSD-Medical Center and is a member of Neuropsychological Associates.

Robert Chen, MA, MBBChir, MSc, FRCPC (Neurologist, rTMS expert)
Dr. Chen is a Professor of Neurology at the University of Toronto. He is an expert of rTMS in both clinical application and basic science research.

Ronghui Xu, Ph.D. (Biostatistician)
Dr. Xu is the current Director of Biostatistics at the UC San Diego, Clinical and Translational Research Institute. She is experienced in analyzing data from large-scale clinical trials.

The members of the DSMB will meet on an as needed basis. Given the geographical location difference and lack of other local experts in rTMS, Dr. Chen will join the board meeting via teleconference. If a serious AE or UPR occur, then the members of the DSMB will be contacted by the PI and a meeting will be set up to address the situation as soon as possible.

The members of the DSMB will not have access to the subject identifying information when reviewing adverse events, and will only be presented with the unique study number.

SAFETY MEASURES IN RESPONSE TO COVID-19
The following safety measures will be used to reduce risk and compliance is to be documented at each On-site visit: screening for COVID-19, PPE, hand washing, reduced staff and scheduling, and sanitization of equipment. A checklist will be used to document that all safety measures are followed and has been attached to the protocol revision.

COVID-19 Screening:

During consent/screening call, subjects will be screened for COVID-19 with the questions provided by the research office to be enrolled in the study:
1. Do you have:
a. A Fever
b. New or worsening cough or shortness of breath
c. Flu-like symptoms

2. Have you or a close contact travelled to an area with community transmission of COVID-19 within the past 21 days? For example, including but not limited to Europe, the middle east, Asia, and/or areas of the United States with significant spread of COVID 19, such as Washington State, New York, Massachusetts and Northern California

3. Have you been in close contact with someone, including health care workers, confirmed to have the coronavirus disease?
Subjects who answer "no" to all questions will be enrolled in the study. Should a subject answer

that they have had symptoms of COVID-19, they will be advised to come into the hospital for testing and a negative test (or confirmation that they are no longer positive) will be required before enrollment.

1-2 days before an on-site visit, subject will be contacted via phone call to screen for COVID symptoms. On arrival at site, screening will be conducted at the entrance of the hospital and when entering the lab for their appointment. Subjects will also be required to have their temperatures check with an IR thermometer. If all symptomology is negative, subjects will be enrolled/allowed to continue with their visit.

If a subject indicates moderate to severe symptoms, subjects will be required to report to the COVID-19 triage for testing. If a subject indicates mid symptoms, such as low fever or only one symptom, and the VA is unable to provide testing, subjects will be asked to stay/return home and will be provided with a COVID-19 home testing kit. If positive results, subjects will be asked to stay home for at least 14 days and seek medical attention through their primary care provider. Subjects may continue with the study after 2 weeks of quarantine or with note from their care provider that they are no longer positive for COVID-19 and under the discretion of the PI. If the subject is unable to meet the study timelines due to COVID-19 the subject may be withdrawn from the study under the discretion of the PI.

Any staff in contact with the subjects will be asked to return home, monitor for COVID-19 symptomology, and tested for COVID-19 with home kit. If test is positive and staff shows symptoms, medical care should be sought and staff are to stay home until they are healthy. If test is positive but employee is asymptomatic, staff should stay quarantined for 2 weeks. If the test is negative, staff should stay at home for 2-5 days to ensure before returning to work as a safety precaution. Staff will also be screened by the hospital when reporting to duty each day.

PPE/Handwashing
Subjects will be required to wear a face mask, wash or use hand sanitizer (before and after visit), and wear gloves (provided by the lab) during the visit. Staff will be required to wear a face mask, eye protection, gloves, disposable gown, and ensure hands are washed before and after each appointment.

Reduced Staff and Scheduling
On-site staff will be limited to 2 study coordinator and the PI and in-person interactions with subjects will be limited to one study coordinator and the PI. Only one subject will be enrolled per week, at least a 30-minute window between each appointment, and only 2 subjects will be in the treatment phase at a given time with alternating treatment schedules.

Sanitization
Equipment must be wiped down with antiseptic cloth before and after each visit which includes the treatment machine, coil, chair, the neuronavigation equipment (pointer, headband, and clicker), laptop, mouse, EMG wires, MVAS sliding scale, door handles, desk, and any other surfaces that may come into contact with patients and staff. In addition, pillowcases and any sheets used will be changed after each subject.

UCSD Keck MRI Center
The UCSD MRI Center has also implemented increased safety measures that include: screening for COVID-19, wearing face masks, washing hands, limiting study team to 1 operator and 1 assistant, mandatory 30 minute gap between appointments, disposable gloves to be work by staff and subject once inside MRI center, sanitization of all equipment before and after scanning, and documenting all safety measures. The regulations implemented by the MRI center has been attached to the protocol revision.

Section 9.12 Off Station Activities

9.12) Describe each off-station activity including where it occurs, subject involvement, and any additional required protections. ***Note: if the off-station activity is being conducted under the approval authority of another institution, this is not VA offsite research and should be described as collaborative research effort. Please contact the HRPP office if you have any questions***

Brain anatomical and functional MRI will be performed within 72 hours after Visits 2 and 13. These scans will be conducted at the Center for Functional MRI (CFMRI)at the UC San Diego School of Medicine. The Study Coordinator will be MRI Operator certified through the center and will conduct the scans. This is the only off-station activity.

Section 10 - Human Subjects

10) Describe the characteristics of the proposed subject population. Include age, gender, ethnicity, and health status as appropriate. ***Note: Data about people are still considered "human subjects" by the IRB, so even if you do not intend to contact the patients whose charts you will review, you still describe the characteristics related to the subjects whose charts you will review.***

- **Provide inclusion and exclusion criteria as appropriate. Provide a statement how non pregnancy is confirmed if pregnancy is an exclusion criteria.**
- **For multisite studies, provide the total number of subjects from all sites and include description of the local site's role as a coordinating center if applicable.**
- **Indicate the number of VA participants to be studied.**
- **Indicate the estimated number of consented subjects that will fail the screening process, if any.**

Number of Participants: 200

Inclusion:

The following diagnostic criteria for MTBI based on the 1993 American Congress of Rehabilitation Medicine and recent recommendation from the DOD, and the current diagnostic criteria adopted by the VASDHS TBI Clinic will be used for the study [67]:

A traumatically induced physiological disruption of brain function, as manifested by at least one of the following: 1) any loss of consciousness; 2) any loss of memory for events immediately before or after the accident; 3) any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused) and focal neurologic deficit (s) that may or may not be transient but where the severity of the injury does not exceed the following: 1) loss of consciousness of approximately 30 min or less; 2) after 30 min, an initial Glasgow Coma Scale score of 13–15; and 3) post-traumatic amnesia not greater than 24 hrs.

In addition, the following established diagnostic criteria for " Persistent headache attributed to mild traumatic injury headache" based on the International Classification of Headache Disorder (ICHD-3)[57] will be applied to the study subjects:

A. Any headache fulfilling criteria C and D
B. Traumatic injury to the head has occurred
C. Headache is reported to have developed within 7 d after one of the following:
1. injury to the head
2. regaining of consciousness following the injury
3. discontinuation of medication(s) that impairs the ability to sense or report headache following the injury
D. Headache persists for >3 mo after injury to the head
E. Not better accounted for by another ICHD-3 diagnosis

Additional Inclusion Criteria:
1. male or female age between 18 to 65;
2. no prior experience of TMS treatment;
3. average persistent headache intensity more than 30 on the 0-100 mechanical visual analog scale(M-VAS) at the screening visit (visit 1)[64] and average persistent headache intensity score greater than 3/10 on a numerical rating scale (NRS) reported in the headache diary (between visits 1&2);
4. no history of daily persistent headache prior to the MTBI incidence:

Exclusion
1. pregnancy; To be eligible for the study and to ensure no pregnancy risk, you will need to utilize contraception or practice abstinence until your study participation is completed
2. history of pacemaker implant; any ferromagnetic material (e.g. bullet fragment, shrapnel, device implant) in the brain or body that would prohibit the patients from having a brain MRI;
3. history of dementia, major psychiatric or life threatening diseases;
4. presence of any other chronic neuropathic pain states;
5. history of seizure;
6. pending litigation;
7. lack of ability to understand the experimental protocol and to adequately communicate in English;
8. history of chronic headache diagnoses such migraine, tension or cluster headaches prior to the incidence of MTBI.

9. history of chronic headache prior to the MTBI incidence at a frequency more than once a month lasting more than one hour.
10. evidence in the chart of recent exacerbation of depressive or anxiety symptoms, active substance dependence, suicidal intent or attempt within
the previous month, and/or current psychotic symptoms

Medications:

Medications allowed during the study will include stable (been used at least 30 days prior to the screening visit) regimens of:

1) Non-narcotic analgesics such as non-steroidal anti-inflammatory, acetaminophen, tramadol, Aspirin.
2) Antidepressants such as Serotonin Specific Reuptake Inhibitors and Tricyclic Antidepressants used mainly for sleep only;
3) Anxiolytics/benzodiazepine hypnotics such as Alprazolam, lorazepam, triazolam used at bedtime only;
4) GABA-A partial agonists/non benzodiazepine hypnotics such as Zolpidem, eszopiclone used for sleep only.

Subjects who receive any narcotic based analgesic, steroid and local anesthetic injection in the peri-scalp region, triptans, anticonvulsants, and antipsychotic medications less than 7 days prior to the pre-treatment assessment will not be enrolled for the study. Non-pharmacologic treatments, including but not limited to, transcutaneous electrical nerve stimulation unit (TENS), acupuncture, acupressure and therapeutic massage above the neck will be prohibited during the entire study. Subjects should not have elective surgery or elective interventional medical procedures for the duration of the study. Subjects are allowed to use additional acetaminophen (up to a maximum total of 3g per day) as the only rescue medication during the study. The use of the rescue and other concomitant medications will be documented in the daily pain log.

Section 10.1 Non-Veteran Subjects

10.1a) Recruitment of non-Veterans cannot be for the sake of convenience for this study. Provide the objective and justification for the inclusion of non-Veteran subjects. Identify how the research results will be generalizable to the Veteran population. ***NEW: ORD now requires completion of a Request to Enroll Non-Veterans form (available in the help section of OnRAMP) for any VA studies requesting to enroll non-Veterans. This form will be reviewed by the local RDC before the application may be considered by the IRB. Complete the form and upload with this submission.***

The only non-veteran subjects that would be included would be those that are considered still active military personnel.

10.1b) Non-Veterans must be given a copy of the VA Notice of Privacy Practices (NOPP) and sign the acknowledgement form when their health information is used/collected for research purposes. In addition, the Privacy Officer must be notified of the non-Veteran enrollment and be provided with a copy of the signed NOPP, when applicable. If CPRS notes are entered, and the acknowledgement must also be scanned into CPRS. ***The NOPP, Acknowledgement form, and instructions to provide the completed form to the PO are available under the ? at the top right corner of this page.***

(•) Agree ( ) Disagree

Section 11 - Recruitment

11) Describe, step-by-step, the plans for recruitment of subjects (or selection of subjects as in record review). This description must include how, when, and where potential subjects are approached as well as procedures for identifying potential participants (through medical records, physician referral, third-party sources, etc.). Include how selection is equitable. Indicate if vulnerability to coercion may be present and if so plans to ensure voluntary participation.

Patients are identified for the study via four ways:

1: Subjects will be recruited from the TBI, Anesthesia Pain Clinic and Neurology TBI Headache Clinic at the VA San Diego Healthcare System (VASDHS)

Patients are referred and evaluated for the rTMS treatment, they are offered the opportunity of study participation with the understanding that they have the option of not participating in the study and still receive clinical treatment protocol.

Veterans referred for possible rTMS treatment are being evaluated during regular clinic visits. The PI and other qualified providers (co-investigators) will evaluate the patient for the treatment based on their medical conditions. If they are determined to be good candidates for the treatment, the nature of the clinical (non-research) treatment protocol, and the risk and benefits of the treatment will be explained and discussed to the patient. In addition, patients will be offered the opportunity of participating in the IRB approved research protocol. The providers will emphasize to the patients that their decisions of study participation will not interfere with their regular care. If they decide not to participate in the study protocol, they can still receive the rTMS treatment via the clinical treatment protocol during regular Anesthesia TMS procedure clinic hours. If a patient expresses interest in the study and agrees to meet the study coordinator, the PI or other qualified providers will contact the study coordinator to come meet the potential patient subject for study informed consent.

2:Patients respond to study flyers

For subjects responding to advertisements who are not patients of the PI or other qualified providers, the appointment will be scheduled by the study coordinator receiving the telephone calls from the potential subjects. The study coordinator will obtain the consent from the patient before screening data are collected. The subjects will also medically be evaluated by the PI or other qualified providers to determine whether their medical conditions meet the study inclusion and exclusion criteria. Before subjects are entered into this study, the purpose and nature of the study as well as possible adverse effects will be explained to them in the presence of a witness. The subject must sign a statement, which complies with the requirements of the US Code of Federal Regulations. A signed original should be given to the subject. With study informed consent signed, the PI will review all the screening information with the study coordinator to determine whether the patient meets the study inclusion or exclusion criteria for enrollment.

3. Naval Medical Center San Diego (NMCSD) flyer recruitment from the C5 and Pain Clinic. Same process as recruitment from the VASDHS flyer/brochure method, the Study coordinator will be contacted by the interested subjects on the designated research phone. A separate IRB approval will be obtained from the NMCSD for the sole purpose of posting recruitment flyers and handing out study brochures to the clinics. There will not be any patient screening needed at NMCSD, no research activities will take place there either. The research study is independent of an IRB recruitment flyer approval through the NMCSD. Brochures will be given to those that might be interested to see if they are eligible and flyers posted in designated areas. The NMCSD is considered a non-VA research collaborator for allowing brochures / flyer distribution if approved through their IRB for that recruitment method.

4. In order to boost recruitment, we plan to contact veterans who have enrolled in the VA IRB approved registry, VASDHS TBI/PTSD Registry - H170023, allowing themselves to be contacted by future VA IRB studies. In section 12.10, we ask for a waiver of partial HIPAA so we can contact the Veteran via their preferred method of contact. If, at any time, the Veteran enrolled in the VASDHS TBI/PTSD Registry lets this study know that they want to withdraw from the registry and no longer want to be contacted, we will contact H170023's study coordinator as soon as possible.

5. A letter will be mailed to potential veterans from the TBI, Anesthesia Pain Clinic, Neurology TBI Headache Clinic, and the VASDHS TBI/PTSD Registry for recruitment which describes the study and asks for a response indicating whether they are interested or not.

6.We will also receive referrals from other VA studies. These studies will provide referrals of veterans who have consented to be contacted for additional studies. Studies we will recruit from include protocol numbers H190062, H160089, and H190078. Subjects from these studies who appear to be eligible for participation in this study and who have consented to be contacted about future research opportunities will be sent a recruitment letter via mail prior to contact by phone unless they have specifically consented to phone contact.

Children and Women

No children will be recruited for this study. The VA requires a waiver for a research on children and currently VASDHS does not offer a pediatric service. Female veterans who meet the study

inclusion and exclusion criteria will be recruited. Female Veterans at child bearing age will be required to have a urine pregnancy test (ordered by the PI) prior to the enrollment.

Section 11.1 Recruitment Materials

11.1) Identify all recruitment materials (flyers, advertisements, letters, etc.) that will be used; include the web address for any web-based advertisements. The text of all communications with prospective participants must be reviewed and approved by the IRB before it can be used. You will be reminded to attach copies of recruitment materials to the initial submission packet. ***Note: Posting of flyers with pull tabs is not permitted within VASDHS (including the VMRF building). However, you may request to advertise on the e-boards (located at the elevators and throughout the facility) or on the VASDHS Research Opportunities web-page.***

A recruitment flyer will be utilized for posting in approved VASDHS areas. A letter will be mailed to potential subjects describing the study.

Section 12 - Informed Consent

12) Indicate whether or not each category of consent is involved in this study:

12a) Will the study team obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without (or prior to) obtaining informed consent of the prospective subject or the prospective subject's LAR?

(•) Yes ( ) No

Check one or both of the below boxes if they apply to this study:

Information will be obtained through oral or written communication with the prospective subject or the subject's Legally Authorized Representative (LAR) and this is not a FDA regulated study.

( ) Yes (•) No

Identifiable information or biospecimens will be obtained by accessing records or stored identifiable biospecimens and this is not an FDA regulated study.

( ) Yes (•) No

Since both boxes were checked "no", a request for an informed consent waiver is needed.

12b) **Signed** informed consent

(•) Yes ( ) No

12c) Waiver of documented consent (e.g., **oral** consent) for all or part of the study.

( ) Yes (•) No

12d) Request for a **waiver** of consent for all or some study activities.

(•) Yes ( ) No

12e) Alteration of **other required elements** of consent.

( ) Yes (•) No

12f) **Child** assent to participate (Director approval will be required)

( ) Yes (•) No

12g) Will any language **other than English** be used by those obtaining consent and understood by the prospective participant or the legally authorized representative?

( ) Yes (•) No

12h) **Decisional Capacity Assessment** to determine if participants have the capacity to consent for themselves.

○ Yes ◉ No

12i) **Surrogate** consent (legally authorized representative)

○ Yes ◉ No

Section 12.1 Informed Consent Process

12.1a) Will consent be obtained before any study procedures are performed (including screening procedures except screening procedures with Consent and/or HIPAA waiver when required)?

◉ Yes ○ No

12.1b) Will the information being communicated to the participant or legally authorized representative during the consent process include exculpatory language through which the participant or legally authorized representative is made to waive or appear to waive any of the participant's legal rights or release or appear to release the Researcher, Sponsor, the VA or its agents from liability for negligence.

○ Yes ◉ No

12.1c) A master list of all VA subjects consented (written or not) under this protocol will be maintained.

◉ Agree ○ Disagree

12.1d) Identify the circumstances under which consent will be obtained including where the process will take place; any waiting period between describing the research and obtaining consent including sufficient time for the prospective participant to consider participation, and any steps taken to minimize the possibility of coercion or undue influence.

Consenting will take place at the VASDHS in Building 23 Room 105 and 108. This is designated research space under the PI. The waiting period between describing the research and obtaining consent is dependent on the potential subject and when they are able to schedule a time with the Study Coordinator to be consented.

Section 12.4 Waiver of Informed Consent

12.4a) Is it practicable to conduct the research without the waiver or alteration of consent?

○ Yes ◉ No

12.4b) Does the research examine public benefit or service programs and is subject to state or local government approval?

○ Yes ◉ No

12.4c) Will the research involve greater than minimal risk?

○ Yes ◉ No

12.4d) Will waiving or altering informed consent adversely affect the subjects' rights and welfare?

○ Yes ◉ No

12.4e) Is it appropriate to provide pertinent information to subjects later BUT this information will NOT be provided?

○ Yes ◉ No

12.4f) Identify to what aspects of the study you are requesting a waiver of consent (i.e., full study or specific aspects). Describe the waiver or alteration needed and why it can be granted (include why the research is not practical without the waiver or alteration and how the waiver enables conducting the study).

Waiver of informed consent or alteration of consent elements may be allowed if the IRB documents these findings and approves waiver or alteration.

The waiver of informed consent is requested for recruitment purposes pertaining to pre-screening over the phone. Pre-screening the potential subject by reviewing inclusion/exclusion criteria over the phone ensures that the individual meets the basic requirements before obtaining the individuals name and number to schedule the consenting visit. The ability to pre-screen potential subjects enables the research to be conducted efficiently and without wasting the potential subjects or research staffs time by consenting someone who does not meet the basic inclusion criteria of the study.

12.4g) Explain why the research could not practicably conducted without using identifiable information.

The research could not practically be conducted without pre-screening over the phone for inclusion/exclusion criteria and obtaining the name and number of subjects eligible for the consenting visit. If prescreening
was unable to be done then there would be a lot more consented subjects failing the screen, wasting the time of the research staff involved as well as the veterans coming in for the study.

Section 12.9 HIPAA Authorization

For each category below, indicate whether or not this study involves the indicated process:

12.9a) **Signed** HIPAA Authorization. ***New Template is available in the ? Help section***

◉ Yes ○ No

12.9b) HIPAA waiver to cover the entire study

○ Yes ◉ No

12.9c) HIPAA waiver for recruitment, screening, and/or for a portion of the study.

◉ Yes ○ No

12.9d) HIPAA Authorization or waiver is **not required** for some or all of the study subjects (e.g. no health data).

○ Yes ◉ No

Section 12.10 HIPAA Waivers and Alterations

12.10a) Describe the purpose/nature of the HIPAA waiver or alteration and list specifically, what identifiers and health information are being requested under the waiver/alteration and identify whether the waiver is for access, use, and/or collection of this information.

Referrals from study H170023, the VA IRB approved VASDHS TBI/PTSD Registry, have given their documented oral consent to be contacted by future studies. We request a HIPAA waiver so that we can contact the Veteran via his or her preferred method of contact. In addition, if veterans in our study are interested in being added to the VASDHS TBI/PTSD Registry, their

information can be available. The specific identifiers being collected are the name, preferred contact (phone number or e-mail), age, gender, and whether the Veteran has TBI and/or PTSD. No other demographic information will be collected.

12.10b) The proposed access, use, and/or disclosure of PHI involves no more than a minimal risk to the privacy of individuals.

◉ Agree ○ Disagree

12.10c) The plan to protect the identifiers from improper use and disclosure is adequate.

◉ Agree ○ Disagree

Describe the plan

The identifiers will be kept on an electronic call log behind the VA firewall so that it can be referenced if needed for call backs or reminder texts. The information will be deleted if no longer needed, and only kept if the potential subject gets consented. The only PHI collected at pre-screen phone call is name and phone number and inclusion/exclusion criteria for reference when coming in for the consenting and full screening visit.

12.10d) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

◉ Agree ○ Disagree

12.10d2) Describe the plan:

Identifiers that are not needed for research will be deleted immediately. There will be no hardcopy versions.

12.10e) By signing this protocol for submission, the PI is providing written assurance that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by the Privacy Rule. 38 U.S.C. 7332 Information: If the waiver of HIPAA authorization is for the use of 38 USC 7332 information (applicable to drug abuse, alcohol abuse, HIV infection, and sickle cell anemia records), by signing this protocol for submission the PI is providing written assurance that the purpose of the data is to conduct scientific research and that no personnel involved may identify, directly or indirectly, any individual patient or subject in any report of such research or otherwise disclose patient or subject identities in any manner. (Ref: 38 U.S.C. 7332(b)(2)(B))

◉ Agree ○ Disagree

12.10f) The research could not practicably be conducted without the waiver or alteration.

◉ Agree ○ Disagree

12.10f2) Describe how the waiver/alteration enables the research to be conducted

The waiver/alteration enables the research to conduct more efficiently so that the researchers can do a pre-screen on the phone to see if the potential subject sounds eligible. The only PHI collected are their name and phone number and inclusion/exclusion criteria. It allows the researchers to follow up with them if they want to schedule at a later date, have a call back or need a reminder text for a consenting visit.

12.10g) The research could not practicably be conducted without access to and use of the PHI.

◉ Agree ○ Disagree

12.10g2) Describe why it would be impracticable to conduct this research without the PHI described 12.10a. (v3 /8/18)

Research could not be conducted without the phone number and documented name of the individual prior to consenting as no confirmation text or contact could be given, thus making it difficult to coordinate meeting the potential subject in person when they do come in. In addition, if inclusion /exclusion criteria are unable to be asked during the pre-screening, then a lot of individuals will have wasted their time if they come in for consenting to find out during the full screen that they were not eligible on criteria that could have been asked before coming in. Asking questions over the phone regarding inclusion/exclusion ensures that the research is done efficiently, and time is being respected.

Section 13 - Alternatives to Participation

13) Describe the alternatives to participation in this research study (see ? for guidance)

If the potential subjects are not interested in participating in the research study, they can discuss alternatives with their primary care physician. If they are patients of the co-investigators or PI they can be referred to receive rTMS treatment via the clinical treatment protocol during regular Anesthesia TMS procedure clinic hours.

Section 14 - Potential Risks

14) Describe any potential or known risks or discomforts and assess their likelihood and seriousness (see ? for guidance)

Risks associated with Repetitive Transcranial Magnetic Stimulation (rTMS) are minimal. A potential side effect of rTMS is a mild headache or headache increase, resulting from muscle stimulation on the scalp. Typically, the headache will resolve spontaneously a few hours after the treatment or with a dose of acetaminophen. Occasionally, skin irritation can occur. This occurrence will be dealt with conservatively. Noise during treatment may also be a concern. However, all subjects will be required to wear earplugs during the treatment session. Some patients may experience sleep disturbance during the course of rTMS or a feeling of increase /decrease of energy level. Although seizure occurrence was reported in the past, to the best knowledge of the investigators, no seizure occurrence has been reported with treatment setting similar to the proposed treatment protocol since the introduction of standard treatment guideline in 1998. These and other risks of the intervention will be fully discussed with the subjects prior to the study and side effect will be assessed during the study as well. Since the MRI scan room consists of strong magnetic field, instruction will be given to each subject prior to entering the scan room so that no subjects with any metal denture, implanted metal device such as aneurysm clips, cardiac pacer or spinal fusion rods will be allowed to enter the scan room. A screening survey will be conducted as required by the MRI center. The magnet of scanner may cause dizziness, which can be avoided
with slow movement when the subjects are near the scanner. These and other risks of the intervention will be fully discussed with the subjects prior to the study and side effects will be assessed during the study as well.

Section 15 - Risk Management

15) Describe the procedures for protecting against or minimizing any potential risks/discomforts, and the adequacy of resources for conducting the study and resources participants may need as a consequence of the research. When applicable, include detail of the following safety measures: (a) The type of safety information to be collected, including AEs; (b) Frequency of safety data collection; (c) Frequency or periodicity of review of cumulative safety data; (d) Statistical tests for analyzing the safety data to determine if harm is occurring; and (e) Conditions that trigger an immediate suspension of the research. See ? for further requirements.

Protection from Risk

1)All procedures will be performed directly or under the direct supervision of the PI or one of the clinical co-investigators in a controlled hospital setting.

2)Subjects with a history of a cardiac arrhythmia that has led to the placement of a cardiac pacer or defibrillator will be excluded from the study.

3)The PI will review the patients' MRIs or consult with Dr. Roland Lee, a neuroradiologist co-investigator to rule out any lesions or ferromagnetic fragments. If any notable findings are discovered through Dr. Lee, the PI will relay that information to the subject.

4)The rTMS stimulation setting used in the study is within the current safety guidelines. However, if the subject feels that the discomfort is excessive, the study will be stopped immediately.

5)Only the PI and the investigators will have access to the research records. Research records will be kept confidential to the extent provided by law. During the study, the patient's name and identity will not be publicly disclosed without their written permission. The results of this study will likely be published in medical journals or presented at medical meetings. However, the authors can only use the assigned patient number in the article or presentation. All research records and data will be kept in a locked cabinet in the PI's research at a VMRF/VA assigned research facility.

6)Minor complications such as local skin irritation or headache will be managed conservatively with rest and /or oral non-narcotic analgesics. Transient seizure activity will be managed with close neurological monitoring. The PI and the co-investigators are either board certified anesthesiologist or ACLS certified.

Section 17 - Potential Benefits

17) Discuss benefits that may be gained by the subject as well as potential benefits to society in general (see ? for guidance)

Patients with TBI related headache would benefit from the study with potential headache intensity reduction and cognitive function improvement. In addition, the information obtained can potentially explain the cause(s) of their symptoms and guide the development of treatments that can potentially correct the aberrant supraspinal functions leading to their debilitating symptoms.

The outcome of the study can help validate the treatment effect of a novel, non-invasive, low-risk and low cost treatment modality to the general VA patient population.

Section 18 - Risk/Benefit Analysis

18) Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result.

Given that headache can significantly impair a patient's daily function and quality of life and conventional therapy with multiple pharmacological agents usually consist of many side effects, the minimal risk associated with TMS treatment, the risk /benefit ratio in the current study is very low. Therefore, the proposed study can potentially gain crucial knowledge about the utilization of a novel non-invasive therapy for Veterans with MTBI and impairing chronic headache problem.

Section 20 - Compensation for Participation

20) Provide all details and justifications of the compensation plan. See ? for detailed requirements.

To compensate the study subjects for their travel expense and time spent with the study activities, and to maximize subject retention, each subject will be reimbursed $30 for the screening visit (Visit 1) and each of the 10 treatment visits (Visits 3-12). For all the other visits, each subject will receive $50 for each of the 6 assessment visits and 2 MRI visits. For all the visits, we budget a total $730 compensation fee for each subject. The payments will be made directly to their bank account using electronic funds transfer.

Section 21 - Responsibilities and Qualifications

Here are the identified study staff members

Albert Y. Leung, MD

Carl T. Rimmele, PhD, Gregory R. Polston, MD, Jay Pyo, D.O., Lisa L. Lin, MD, Lu D. Le, DO, Michael A. Vaninetti, MD, Paul B. Krug, DNP, RN, Roland R. Lee, MD, Thomas R. Rutledge, PhD, Caleb Lopez, BS, Caleb Lopez, BS, Michael Paul Ho, BS, Talyn Hughes, BS, Valerie G. Le, Shahrokh Golshan, PhD, Michelle Kennedy, BA, Seshagiri Mallina, Valerie G. Le

21) For each staff member listed above, describe their role and qualifications. Also indicate which of the study staff are authorized to obtain consent, when applicable to the study.

Albert Leung, M.D. (AL): Principal Investigator
Dr. Leung is a Clinical Professor of Anesthesiology at the University of California, San Diego (UCSD), a Staff Physician at Veteran Affairs San Diego Healthcare System (VASDHS), and Research Scientist at Veterans Medical Research Foundation (VMRF). He holds joint appointments with UCSD, VASDHS and VMRF. Dr. Leung has served the VASDHS as a staff physician since 1999 and was the Director of the Anesthesia Pain Service from 2001 to 2006. He founded the first Transcranial Magnetic Stimulation (TMS) treatment clinic for treating intractable central pain in the VA system in 2010. The clinic now provides repetitive TMS (rTMS) therapy as an non-invasive therapeutic option for veterans with intractable chronic pain conditions such as MTBI. He has extensive experience in human experimental pain, functional imaging data acquisition and analysis from prior studies. Dr. Leung will assume full responsibility for all activities related to the conduct of the study. He will coordinate the activities of the research team with assistance from the study coordinator. He will assist in data analysis, and outcomes interpretation. He will also take primary responsibility for manuscript preparation for publication. He will present findings at scientific meetings. Dr. Leung will train study personnel on protocol implementation and to standardize evaluation and treatment procedures.

Thomas Rutledge, Ph.D. (TR): Co-Investigator
Dr. Rutledge is a clinical psychologist at the VASDHS. He has extensive clinical and research experience in pain management, depression and PTSD. He will also provide support for the PI and other co-investigators for managing any psychiatric emergency. He will provide training or guidance for the study coordinator to conduct all neuropsychological assessments proposed in the study.

Roland Lee, M.D. (RL): Co-Investigator
Dr. Lee is a neuroradiologist, currently on staff at VASDHS and UCSD. He is the current Director, UC San Diego Magnetoencephalography (MEG) Lab and Chief of Neuroradiology. He and the PI have collaborated in previous studies involving fMRI to assess the central functional response related to TMS treatment. Dr. Lee will provide the PI with clinical and research support for any clinical issues related to MRI interpretation which will be used for neuronavigation guided TMS and neurofunctional imaging data obtained from the study.

Michael Vaninetti, M.D., Co-investigator
Dr. Vaninetti is an Assistant Clinical Professor of Anesthesiology at UCSD. He will assist the PI with the recruitment of study patients, answering of patient questions, delivering treatment to the study subjects, supervising the study coordinator, and making final conclusions about this study.

Lisa Lin, M.D., Co-Investigator
Dr. Lisa Lin is staff physician for Physical and Rehab Medicine at the VASDHS. She has collaborated with the PI before in previous studies. She will be assisting in referrals for recruitment.

John D'Andrea, M.D., Co-Investigator
Dr. D'Andrea is staff physician for Physical and Rehab Medicine at the VASDHS. He will be assisting in referrals for recruitment.

Jay Pyo, D.O., Co-Investigator
Dr. Pyo is the Chief of the Physical Medicine Rehabilitation Service at the VASDHS. He has collaborated with the PI before in previous studies. He will be assisting in referrals for recruitment.

Paul Krug, NP/RN: Co-Investigator
Mr. Krug is the nurse practitioner for the TMS Clinic at the VASDHS. He will be assisting in

referrals for recruitment.

Shahrokh Golshan, Ph.D. (SG): Study Biostatistician
Dr. Golshan is a Project Scientist in the UCSD Department of Psychiatry and the PI and Director of the Methodology, Biostatistics and Data Management Unit for the Advanced Center for Innovation in Services and Intervention Research since 2000. Dr. Golshan will be available to provide statistical and data management consultation during the design, implementation of this study and will be responsible for randomization and will conduct all of the statistical analyses.

Lu D Le, DO: Co-Investigator
Dr. Le is the Medical Director at the Aspire Center for the VASDHS. He will provide support for the PI and other co-investigators for mental health related questions pertaining to the study. He will provide training or guidance for the study coordinator with the neuropsychological assessments proposed in the study.

Carl Rimmele, PHD: Co-Investigator
Dr. Rimmele is the VA ASPIRE Center Director. He will provide support for the PI and other co-investigators for mental health related questions pertaining to the study. In addition, he will provide information regarding the study to veterans who may be interested in participating, giving them the study coordinator contact information for follow up.

Michelle Kennedy, B.A.: Lab Manager
Ms. Kennedy is well versed in the research environment, has been trained by the PI in the various assessments related to the current proposal. She will be responsible for assisting in the daily operations of the study. She will be able to obtain consent.

Talyn Hughes, B.S.: Study Coordinator / Research Assistant
Ms. Hughes is well versed in the research environment, has been trained by the PI in the various assessments related to the current proposal. She will be responsible for assisting in the daily operations of the study. She will be able to obtain consent.

Valerie Le, BS; Study Coordinator
Ms. Le will be responsible for assisting the study coordinator with research activities, including recruiting, consenting, administering neuropsychological assessments, assisting with study treatments, and follow up visits. She was previously a volunteer at the lab for 2 years and is familiar with human subject research. She has been trained by the PI and current study staff.

Michael Ho, BS; Study Coordinator
Mr. Ho will be responsible for assisting the study coordinator with research activities, including recruiting, consenting, administering neuropsychological assessments, assisting with study treatments, and follow up visits. He has been trained by the PI and current study staff.

Caleb Lopez, BS; Clinical Research Associate
Mr. Lopez is well versed in the research environment, has been trained by the PI in the various assessments related to the current proposal. He will be responsible for assisting in the daily operations of the study. He will be able to obtain consent.

Seshagiri Mallina; Research Associate
Mr. Mallina is well versed in the research environment, has been trained by the PI in MRI analysis related to the current proposal. He will primarily assist with MRI-related tasks for this study including processing, analysis and running of scans.

Section 22 - Bibliography

22) List relevant articles that the IRB can use to provide necessary background for the protocol. Do not include an extensive NIH-grant-style bibliography. (Up to 5 recommended, but use more if needed to support the protocol or citations above.)

Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D, Devanne H, Di Lazzaro V, Filipovic SR, Hummel FC, Jaaskelainen SK, Kimiskidis VK, Koch G, Langguth B, Nyffeler T, Oliviero A, Padberg F, Poulet E, Rossi S, Rossini PM, Rothwell JC, Schonfeldt-Lecuona C, Siebner HR, Slotema CW, Stagg CJ, Valls-Sole J, Ziemann U, Paulus W, Garcia-Larrea L. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014; 125(11):2150-2206.

Leung A, Shukla S, Fallah A, Song D, Lin L, Golshan S, Tsai A, Jak A, Polston G, Lee R. Repetitive

Transcranial Magnetic Stimulation in Managing Mild Traumatic Brain Injury-Related Headaches. Neuromodulation 2015.

Neville IS, Hayashi CY, El Hajj SA, Zaninotto AL, Sabino JP, Sousa LM, Jr., Nagumo MM, Brunoni AR, Shieh BD, Amorim RL, Teixeira MJ, Paiva WS. Repetitive Transcranial Magnetic Stimulation (rTMS) for the cognitive rehabilitation of traumatic brain injury (TBI) victims: study protocol for a randomized controlled trial. Trials 2015;16:440.

Patil VK, St Andre JR, Crisan E, Smith BM, Evans CT, Steiner ML, Pape TL. Prevalence and treatment of headaches in veterans with mild traumatic brain injury. Headache 2011;51(7):1112-1121.

Tallus J, Lioumis P, Hamalainen H, Kahkonen S, Tenovuo O. Long-lasting TMS motor threshold elevation in mild traumatic brain injury. Acta Neurol Scand 2011.

Section 23 - Sponsors and Collaborators

23) Clarify any industry financial or other support (e.g., NIH funds the study or Company X provides the assay kits). Identify non-VA Research collaborators and their role in this protocol, including whether or not they have access to subjects or identified data.

Dr. Alireza Salami is an assistant professor through the Department of Neurobiology at the Karolinska Institute, Stockholm, Sweden. He has a PhD in Computational Neuroscience and will assist the study staff in understanding functional magnetic resonance imaging data analysis. He will not have access to subjects or identified data.

In the submission form, upload a copy of the grant, subaward, CRADA, etc. as appliable to the study.

Section 27 - Privacy, Confidentiality, and Information Security

27a) Provide a brief description of how participant privacy and confidentiality will be protected in this study. Describe the circumstance under which it may be possible for a research team member to identify subjects and any related protections or assurances to prohibit or avoid identification. Describe how the number of people with access to identifiers for research purposes is limited in order to protect a participant's privacy.

Participant information will be kept behind the password protected VA network firewall. In addition, any hardcopies will be locked in both a cabinet and in a locked room in Room 112, 110, 107 of Building 23. There are limited people with access to identifiers in order to protect the participants' privacy.

27.b) Entry of a CPRS Research Informed Consent Note is required when subjects will be admitted as inpatients or treated as an outpatients for research *and* the study involves research medical care or may affect medical care.

- ***If a Research consent Note is required, then a Research Progress Note should also be entered for each procedure or intervention.***
- ***Scanning the Consent and HIPAA Authorization into CPRS is not required. Linking the Consent to the Research Informed Consent Note may be permitted and can be useful for trials involving the Research Pharmacy or when research will be performed in conjunction with clinical procedures.***
- ***For Non-Veterans, if Research Informed Consent Notes are entered, then the NOPP Acknowledgment must be scanned into the record. Otherwise a copy of the signed NOPP must be retained with the Investigator's research records and a copy sent to the Privacy Officer; see the ? Help for more information.***

27.b1) Is entry of CPRS notes required based on the above criteria?

- (•) CPRS notes are needed for ALL subjects
- ( ) CPRS notes are needed for SOME subjects
- ( ) CPRS notes are NOT needed for any subjects

27c) Select the VA Sensitive Information (VASI) use category

- ○ This study does not collect or use any VASI
- ○ This study uses but does not save, collect, copy, or record VASI
- ◉ This study does collect or record VASI

Section 27.1 VA Sensitive Information (VASI)

27.1a) For each type of VASI, indicate all that apply:

Indicate which of the following will be collected/recorded:

- ☑ Protected Health Information (PHI)
- ☑ Names
- ☐ Device identifiers and serial numbers
- ☑ E-mail addresses
- ☐ Medical record numbers
- ☐ URLs (Universal Resource Locator)
- ☐ All elements of dates (except year) or any age over 89
- ☐ Health plan beneficiary numbers
- ☐ IP Addresses (Internet Protocol)
- ☑ Telephone numbers
- ☐ Account numbers
- ☐ Biometric Identifiers including finger and voice print
- ☐ Fax numbers
- ☐ Certificate or license numbers
- ☐ Full face photographic images and comparable images
- ☐ All geographic subdivisions smaller than a state
- ☐ Vehicle ID and serial numbers including license plate numbers
- ☑ Social security numbers or scrambled SSNs (describe below)
- ☐ Other unique identifying number, characteristic, or code (describe below)

27.1a1) Describe why SSN are needed for this study

Their SSN will be collected for use with HIPAA compliance and authorization. The last four of their SSN will be stored securely behind the VA firewall with their demographic information on the secured electronic master list of consented subjects.

27.1b) Consent Forms and/or HIPAA Authorization

◉ Yes ○ No

27.1c) Images with personal identifiers are used for this study (x-rays, MRI images with patient names, record numbers, dates, etc.)?

◉ Yes ○ No

27.1c1) Identify where images will be stored (e.g., in the medical record, with study hardcopy records, with study electronic VASI records).

The MRI images collected will be named with the coded subject ID and the date of the MRI. It is stored on secured VMRF server under the PI: Dr. Albert Leung's private data folder.

27.1d) Photos with faces or audio video recordings are used for this study.

○ Yes ◉ No

27.1e) Biological specimens with identifiers are used for this study.

○ Yes ◉ No

Section 27.2 Data Collection, Tools, and Resources

27.2a) Will any specially obtained software be used?

◉ Yes ○ No

27.2a1) Describe the software, and identify license requirements and the ownership of the software or license. Identify on what computer/network the software will be used (e.g., VA, VA Research/VMRF, local hard drive) and any data that will be stored in temporary files on the computer's hard drive

The ANT Neuro Visor2 neuronavigation system will be used during treatment sessions and is specialized software owned by the PI. It is on a stand alone laptop not connected to any network and any data stored in temporary files are anonymized and do not contain any identifiers.

27.2b) Will any mobile devices (laptop, tablet, portable hard-drive, etc.) be used in support of this study?

◉ Yes ○ No

27.2b1) Provide details of the device/s. Indicate whether the device is FIPS 140-2 encryption validated and confirm that the device is listed in the VA EIL. Provide details regarding the nature of the data that will be stored or transmitted on the device and confirm whether a copy of all data will be stored on the VA network.

A laptop will be used to conduct treatment sessions for the study. The laptop is not connected to any network and data is not stored on it. It is merely for visualizing the treatment location during treatment sessions per subject using the Visor2 software. It works with the Visor2 equipment needed for treatment,
the equipment is tagged as EE110005.

27.2c) Does the study require use of an electronic data capture system?

○ Yes ◉ No

27.2d) Will any other web-based applications be used (e.g., for recruitment, completing online questionnaires, or processing data)?

○ Yes ◉ No

27.2e) Will coded data that excludes personal identifiers be used? Coded data excludes *all* HIPAA identifiers (per VHA Handbook 1605.1 Appendix B), including dates

◉ Yes ○ No

27.2e1) Identify where the code key is stored and in what format (electronic, paper).

The electronic master list of consented subjects holds the date of consent, demographic information, names and subject ID.

Section 27.3 Data Sharing and Transportation

27.3a) Does this study involve collecting, sharing or transporting any type of data outside of the local VA?

◉ Yes ○ No

27.3b) This study collects VASI outside of VA (i.e., at a non-VA location).

◉ Yes ○ No

27.3b1) Describe what is collected outside the VA and how it is secured in transit back to the VA. *Note: An approved Authorization to Transport will be required.*

The MRI images are collected at the UCSD Keck Imaging center where the date of the scan is the only identifier. It is directly transferred to the UCSD server for download on the VA premises. There is no physical transportation of data. This process has been approved in previous studies, see H160047 for
reference.

27.3c) VASI is transported outside of VA for any purpose other than sharing.

○ Yes ◉ No

27.3d) PHI may be disclosed to monitoring/auditing agencies by HIPAA Authorization. ***Note: The Research Office must be notified when monitors come to audit***

◉ Yes ○ No

27.3e) Data may be shared with collaborators or others in the conduct of this protocol.

○ Yes ◉ No

Section 27.4 Research Record Storage and Retention

For each type of record, indicate whether it is collected for this study

27.4a) Hardcopy records/data (includes paper, pictures, film, etc.)

◉ Yes ○ No

27.4a1) Identify precisely where hardcopy data will be stored to include physical site, building, and room number, etc. For each location identify whether VASI or non-sensitive information is stored at that location. For VASI, identify how the data is secured.

Hardcopy data will be stored in Building 23, Room 112, 110, 107, 108. VASI to include hardcopy consent documents will be stored separate from hardcopy data folders, in a locked cabinet in Room 112, 110, 107, 108.

27.4a2) Are all of the above locations at VA?

◉ Yes ○ No

27.4b) Electronic study records (includes computer files, removable disk files, digital files, etc.).

◉ Yes ○ No

27.4b1) Identify precisely where ***non-sensitive*** electronic records/data will be stored to include the full map drive, network location/server name, etc., and a brief description of what data/information is stored at each location.

R:\Leung\NEW MASTER STUDY FOLDER\1. Master Research Folders\H170053 ---This is where blank assessments will be stored, IRB stamped documents and other anonymized documents. R:\Leung\Access Database ---This is where anonymized data will be stored electronically. It is a microsoft database behind the VA firewall.

27.4b2) Identify precisely where ***VASI*** electronic records/data will be stored to include the full map drive, network location/server name, etc., and a brief description of what data/information is stored at each location.

If no VASI is collected or recorded for this study, simply indicate that the "Study does not collect or record VASI".

R:\Leung\NEW MASTER STUDY FOLDER\1. Master Research Folders\H170053 ---This is where blank assessments will be stored, IRB stamped documents and other anonymized documents.

R:\Leung\Access Database ---This is where anonymized data will be stored electronically. It is a microsoft database behind the VA firewall.

Server: smb://132.239.102.236/Leung ---This is the VMRF dedicated server where the MRI images are stored for backup. The only identifier on these images are the date.

27.4b3) Are any of the locations described in 27.4b outside of the VA Secure Network? *Note: this includes storage on a computer local hard drive.*

○ Yes ◉ No

27.4c) Record Retention - VHA requires compliance with Records Control Schedule (RCS-10) for retention of electronic and hard copy records. Following study closure, these temporary records must be retained for six years and then destroyed. Longer retention may be permitted if required by other Federal regulations or requirements. Will RCS-10 requirements be followed (i.e., 6-year retention)?

◉ I will adhere to VHA Records Control Schedule-10 requirements
○ I request an exception to RCS-10 requirements

Section 27.5 Additional Privacy or Information Security Details

Provide any other privacy or information security details here.

Section 27.6 Attestations

In the event of real or suspected breach of security, the Information Security Officer, Privacy Officer, VA Police (if appropriate), and the individual's supervisor will be notified within one hour of learning of the event.

◉ Agree ○ Disagree

Study staff will be up to date on any required VHA Privacy Policy and Information Security training or they will not be allowed access to VA Sensitive Information.

◉ Agree ○ Disagree

Access to research sensitive information, if any, will be removed when study personnel are no longer part of the research team.

◉ Agree ○ Disagree

At least one copy of all study records (whether sensitive or non-sensitive) will be retained under VA control and only destroyed in compliance with the approved Records Control Schedule

◉ Agree ○ Disagree

The VA retains ownership of the research data. Should the investigator leave the VA, custody of the research records will be assigned to another investigator and the Research Service notified in writing, or custody of the research records will be transferred to the Research Service.

◉ Agree ○ Disagree

Section 28 - Protocol Association to New or Existing Project

28) Is this a new R&D Project? Before you go on to complete the *Initial Review Submission Form* (which is used for attachments), please address the association of this Protocol to an R&D Committee Project. This Protocol may represent a new R&D Project, or it may be an additional Protocol under an existing R&D Project (such as when a single grant supports multiple Protocols). Will this Protocol be submitted to the R&D Committee as a new Project?

○ Yes ◉ No

Section 29 - Existing Project Association

29) The associated R&D Project should already exist in the database. Identify the R&D Project(s) that correspond to this protocol.

Project Status	Proposal Number	Project Title	Principal Investigator
No Projects are Linked to this Study			

The Protocol Application is now complete for a Protocol attached to an existing Project.

Next you will go on to the Initial Review Submission Form. This form is used to collect the Application and any other needed attachments for submission to the IRB for review.

Press *Save and Continue*