Passive electrical neurofeedback treatment of mTBI: MEG and Behavioral Outcomes

NCT03244475

July 9, 2023

Human Protocol (Version 1.32)

General Information

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

Passive Electrical Neurofeedback Treatment of mTBI: MEG and Behavioral Outcomes

***Please provide a short name (nickname) to reference this protocol::**

Neurofeedback MEG Veterans Study
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Add departments

and Specify Research Location:

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

Identify protocol staff members

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

Huang, Mingxiong, PhD

3.1 Add all other VA research staff personnel (if name is not in the list, please contact Research Staffing to confirm appointment status)

A) Additional Investigators

Baker, Dewleen G., MD
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Harrington, Deborah L., PhD
Co-Investigator
Le, Lu D., DO
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Lee, Roland R., MD
Co-Investigator
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The Research Contact(s) will receive all important system notifications along with the Principal Investigator. (Research Contacts are typically Study Coordinators or the Principal Investigator themselves).

VASDHS IRB
Human Subjects Protocol
v20190121

Section 1 - Preliminaries

Principal Investigator:

Mingxiong Huang, PhD

Protocol Title:

Passive Electrical Neurofeedback Treatment of mTBI: MEG and Behavioral Outcomes

IRB Protocol Number:

H170033

Protocol Nickname:

Neurofeedback MEG Veterans Study

Form Template Version:

v20150115

Date Prepared:

03/02/2023

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).

175

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)

4 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)

Mild traumatic brain injury (mTBI) is a leading cause of sustained physical, cognitive, emotional, and behavioral deficits in OEF/OIF/OND Veterans and the general public. However, the underlying pathophysiology is not completely understood, and there are few effective treatments for post-concussive symptoms(PCS). In addition, there are substantial overlaps between PCS and post-traumatic stress disorder (PTSD) symptoms in mTBI. IASIS is among a class of passive neurofeedback treatments that combine low-intensity pulses for transcranial electrical stimulation (LIP-tES) with electroencephalography (EEG) monitoring. Nexalin is another tES technique , with FDA approvals for treating insomnia, depression, and anxiety. LIP-tES techniques have shown promising results in alleviating PCS individuals with TBI. However, the neural mechanisms underlying the effects of LIP-tES treatment in TBI are unknown, owing to the dearth of neuroimaging
investigations of this therapeutic intervention. Conventional neuroimaging techniques such as MRI and CT have limited sensitivity in detecting physiological abnormalities caused by mTBI, or in assessing the efficacy of
mTBI treatments. In acute and chronic phases, CT and MRI are typically negative even in mTBI patients with persistent PCS. In contrast, evidence is mounting in support of resting-state magnetoencephalography (rs-MEG) slow-wave source imaging (delta-band, 1-4 Hz) as a noninvasive imaging marker for neuronal abnormalities in mTBI. The primary goal of the present application is to use rs-MEG to identify the neural underpinnings of behavioral changes associated with IASIS treatment in Veterans with mTBI. Using a doubleblind placebo controlled design, we will study changes in abnormal MEG slow-waves before and after IASIS treatment (relative to a 'sham' treatment group) in Veterans with mTBI. For a subset of participants who may have remaining TBI symptoms at the end of all IASIS treatment sessions, MEG slow-wave changes will be recorded before and after additional Nexalin treatment. In addition, we will examine treatment related changes in PCS, PTSD symptoms, neuropsychological test performances, and their association with changes in MEG slow-waves.

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.

Mild traumatic brain injury (mTBI) is a leading cause of sustained physical, cognitive, emotional, and behavioral deficits in OEF/OIF/OND Veterans and the general public. However, the underlying pathophysiology is not completely understood, and there are few effective treatments for post-concussive symptoms (PCS) [23,24]. In addition, there are substantial overlaps between PCS and post-traumatic stress disorder (PTSD) symptoms in mTBI [25]. Furthermore, a substantial number of studies have shown higher (nearly double) rates of comorbid PTSD in individuals with mTBI, observed in military and civilian settings [26,27]. IASIS is among a class of passive neurofeedback treatments that combine low-intensity pulses for transcranial electrical stimulation (LIP-tES) with electroencephalography (EEG) monitoring [28–30]. LIP-tES techniques have shown promising results in alleviating PCS in individuals with TBI [31–35]. However, the neural mechanisms underlying the effects of LIP-tES treatment in TBI are unknown, owing to the dearth of neuroimaging investigations of this therapeutic intervention. Conventional neuroimaging techniques such as MRI and CT have limited sensitivity in detecting physiological abnormalities caused by mTBI, or in assessing the efficacy of mTBI treatments. In acute and chronic phases, CT and MRI are typically negative even in mTBI patients with persistent PCS. In contrast, evidence is mounting in support of resting-state magnetoencephalography (rs- MEG) slow-wave source imaging as a non-invasive imaging marker for neuronal abnormalities in mTBI [1,2,4,36–39]. Using region of interest (ROI) and voxel-wise approaches, we demonstrated that MEG slowwave source imaging detects abnormal slow-waves (delta-band, 1-4 Hz) with ~85% sensitivity in chronic and sub-acute mTBI patients with persistent PCS [1,36]. The primary goal of the present application is to use rs- MEG to identify the neural underpinnings of behavioral changes associated with IASIS treatment in Veterans
with mTBI. Using a double-blind placebo controlled design, we will study changes in abnormal MEG slowwaves before and after IASIS treatment (relative to a 'sham' treatment group), and for a subset, before and after additional Nexalin treatment, in Veterans with mTBI. In addition, we will examine treatment-related changes in PCS, PTSD symptoms, neuropsychological test performances, and their association with changes in MEG slow-waves. Pre-treatment baseline and posttreatment rs-MEG exams, symptoms assessments, and neuropsychological tests will be performed. We for the first time will address a fundamental question about the mechanism of slow-waves in brain injury, namely
whether slow-wave generation in wakefulness is merely a negative consequence of neuronal

injury or if it is a signature of ongoing neuronal rearrangement and healing that occurs at the site of the injury.

Specific Aim 1: To detect the loci of injury in Veterans with mTBI and assess the mechanisms underlying functional neuroimaging changes related to IASIS treatment, and for a subset of Veterans with remaining symptoms, additional Nexalin treatment, using rs-MEG slow-wave source imaging. Our voxel-wise rs-MEG source-imaging technique will be used to identify abnormal slow-wave generation (delta
band) in the baseline and post-treatment MEG exams to assess treatment-related changes on a single-subject basis. Healthy control (HC) Veterans, matched for combat exposure, will be used to establish an MEG normative database. Test-retest reliability of MEG slow-wave source imaging for mTBI will also be examined.
Hypothesis 1: Veterans with mTBI will generate abnormal MEG slow-waves during the baseline MEG exam. Voxel-wise MEG slow-wave source imaging will show significantly higher sensitivity than conventional MRI in identifying the loci of injury on a single-subject basis. The test-retest reliability of MEG slow-wave source imaging is expected to be high, with intra-class correlation coefficient (ICC) ≥ 0.75 between two sequential MEG exams.
Hypothesis 2: In wakefulness, slow-wave generation is a signature of ongoing neural rearrangement/ healing, rather than a negative consequence of neuronal injury. IASIS treatment will enhance neural rearrangement/healing by initially potentiating slow-wave generation immediately after each treatment session.
Hypothesis 3: IASIS will ultimately reduce abnormal MEG slow-wave generation in mTBI by the end of the treatment course, owing to the accomplishment of neural rearrangement / healing. In Veterans with mTBI who finish IASIS treatment, but not in the sham group, MEG source imaging will show a significant decrease in
abnormal slow-waves at post-treatment exam. Such significant decreases will also be evident in both the voxel-wise and overall abnormal MEG slow-wave measures.

Specific Aim 2: To examine treatment-related changes in PCS and PTSD symptoms in Veterans with mTBI. PCS and PTSD symptoms will be assessed at the baseline and post-treatment follow-up visits.
Hypothesis 4: Compared with the sham group, mTBI Veterans in the IASIS treatment group will show significantly greater decreases in PCS symptoms between baseline and post-treatment assessments.
Hypothesis 5: Compared with the sham group, mTBI Veterans in the IASIS treatment group will also show significantly greater decreases in PTSD symptoms between baseline and post-treatment assessments.

Specific Aim 3: To study the relationship among IASIS treatment-related changes in rs-MEG slow-wave imaging, PCS, and neuropsychological measures in Veterans with mTBI. We will correlate changes between baseline and post-IASIS abnormal rs-MEG slow-wave generation (i.e., total abnormal rs-MEG slow-wave and voxel-wise source imaging measures) with changes in PCS and neuropsychological tests performance.
Hypothesis 6: Reduced MEG slow-wave generation will correlate with reduced total PCS score, individual PCS scores (e.g., sleep disturbance, post-traumatic headache, photophobia, and memory problem symptoms), and improved neuropsychological exam scores between post-IASIS and baseline exams.

Section 7 - Background and Significance

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

B. Background

B.1 Challenges of Neuroimaging Techniques in Detecting Mild TBI

Mild TBI (mTBI) is a leading cause of sustained physical, cognitive, emotional, and behavioral deficits in OEF/OIF/OND Veterans with combat-related exposure to blast as a primary cause. In the general population, the majority (75%) of TBIs are in the “mild” range of severity (mTBI) [24]. A combat-related TBI study showed that 89% of all TBIs were mild [23]. However, the pathophysiology of mTBI is not completely understood, the long-term effects of mTBI are controversial, and there have been few effective treatments for mTBI. Although post-concussive symptoms (PCS) in mTBI resolve by three months after injury in the majority of individuals [40], about 20% (varying from 8-33%) of mTBI patients show persistent PCS and long-term cognitive and/or behavioral impairments [40,41]. It is unclear why similar mTBI events can lead to dramatic neurobehavioral decompensation with persistent PCS in some patients, but not in others [42]. In the majority of acute and particularly chronic mTBI patients, CT and MRI are generally negative [43–45], even in individuals with persistent PCS and cognitive and/or behavioral deficits. This finding highlights the limited diagnostic and treatment-assessment values of

conventional CT and MRI, especially in the chronic phase.

Diffuse axonal injury (DAI) commonly induced by sudden acceleration-deceleration or rotational forces is considered to be a major contributor to PCS and cognitive deficits in TBI patients. In a rodent TBI model, axonal injury was the most prominent feature following blast exposure [46]. In humans, tissue injury is characterized by axonal stretching, inflammation, disruption, and separation of nerve fibers, yet axotomy is relatively rare in even severe TBI [47]. Abnormalities in neurochemical systems such as cholinergic pathways is another signature of TBI [48–50]. Conventional CT and MRI are primarily sensitive to blood from nearby torn capillaries, rather than axonal or neurochemical injury, hence, they underestimate the presence of DAI and/or neurochemical dysfunctions, especially in mTBI patients with persistent PCS.

Diffusion MRI including diffusion tensor imaging (DTI) has been used to examine axonal injury in mild, moderate, and severe TBIs with promising results. In mTBI, reduced fractional anisotropy (FA) was the most frequent finding [51–53]. FA reduction has been attributed to a change in the parenchymal structure, which may include misalignment of fibers, edema, fiber disruption, and axonal degeneration [53,54]. However, increased FA [55] or no change in FA [56] has also been reported in mTBI, signifying a need for more research to delineate DTI parameters and their underlying neuropathology. Notably, DTI has not been used diagnostically due to significant overlap between HCs and mTBI patients in DTI metrics. Thus, the sensitivity is limited (~25-30%) [51,57,58]. An extensive review paper [5] suggests that “DTI techniques are sensitive for mTBI at the group level only, and there is insufficient evidence that DTI plays a role at the individual level.”

Measures of functional connectivity (FC) are also of keen interest in mTBI because they are sensitive to disturbances in the communication amongst brain regions. Although disturbances in FC have been reported in many studies of mTBI, there are large discrepancies in the findings. For example, out of 25 resting-state functional magnetic resonance imaging (rs-fMRI) studies of mTBI reviewed in [14], 6 showed only increased
FC, 9 showed only decreased FC, and 10 showed co-existence of increased FC in some brain networks/regions and decreased FC in other networks/regions . Several rs-MEG studies of abnormal FC in TBI, including our recent paper, also showed increases, decreases, or both increases and decreases in different brain networks / regions [14]. In our study [14], we suggested that aberrant decreases in FC are compatible with the DAI model for TBI, whereas some aberrant increases in FC may be related to compensation or rerouting mechanisms. Thus, multiple mechanisms may underlie disturbances in functional and potentially structural connectivity in mTBI. Similar to DTI studies, studies in mTBI using either rs-fMRI or rs-MEG suggest that FC measures have been in the level of group analysis, not sufficiently sensitive at the single-subject level
for diagnosing mTBI.

B.2 MEG Slow-wave Source Imaging for Sensitive Detection of mTBI

Neurophysiology of abnormal slow-waves: There is an urgent need to develop neuroimaging tools that would aid in the diagnosis of mTBI. This would promote more informed clinical management and decisionmaking in Veterans with persistent PCS, and aid in assessing the efficacy of mTBI treatments. To this end, our MEG source imaging technique holds considerable promise for the detection of subtle pathology that often goes undetected in individuals with mTBI using conventional CT/MRI. MEG is a non-invasive functional imaging technique that directly measures the magnetic signal due to neuronal activation in GM with high temporal resolution (< 1 ms) and spatial localization accuracy (2-3 mm at cortical level) [59]. Rs-MEG is highly sensitive to abnormal neuronal signals resulting from brain injuries. Slow-waves, if present during wakefulness, are a sign of brain dysfunction [13]. Neurophysiological studies in animals have established a solid connection between pathological delta-wave (1-4 Hz) generation in GM and injuries in WM. Polymorphic delta-band slowwaves produced by WM axonal lesions in cats were localized to the GM of cortex overlying the lesion [10,11]. Abnormal delta-waves can also be induced by the administration of atropine in the white matter (WM) [12]. It is known that atropine is a competitive antagonist of acetylcholine (ACh) receptors and can block and/or limit ACh. These animal experiments concluded that cortical deafferentation was a key factor in abnormal deltawave production, owing to WM lesions (i.e., axonal injury) and/or blockages/limitations in the cholinergic pathway [60]. They also demonstrated that abnormal delta-waves can directly result from axonal and/or cholinergic blockage/limitation. Delta-wave-based measurements, such as rs-MEG slow-wave imaging, may be particularly sensitive to both mechanisms, which are two major contributing factors in TBI (Section B.1).

Slow-wave generation during non-REM sleep: Sleep studies further support the relationship between delta-wave generation and cholinergic blockage/limitation. During REM sleep and awake stages, the brain rhythms are dominated by oscillations at a frequency higher than delta waves. However during non-REM sleep stages 3 and 4, delta-waves are the dominant brain rhythm in the brain. ACh is one of the leading neurotransmitters related to sleep. ACh neurotransmitter affects certain cholinergic neurons that are active strongly during periods of REM sleep, but much less so during non-REM sleep and therefore are called REMON cells [61]. The marked reduction/limitation of

ACh release during the non-REM sleep stages 3 and 4 is a key contributor to the pronounced generation of delta waves during those stages [13].

High sensitivity of MEG's slow-wave source imaging in mTBI: Human studies in wakefulness including ours showed that the brains of mTBI patients generate abnormal low-frequency magnetic waves that can be measured and localized by MEG [1,2,4,36–39]. MEG is also more sensitive than conventional MRI or EEG in detecting abnormalities in mTBI patients [38,39]. Unlike normal rs-MEG data, which is dominated by neuronal activity with frequencies above 8 Hz, injured neuronal tissues in many chronic neurological disorders (e.g., head trauma, brain tumors, stroke, epilepsy, Alzheimer's disease, and certain chronic neurovascular diseases) generate abnormal focal or multi-focal low-frequency neuronal magnetic signals (delta-band 1-4 Hz, extending to theta-band 5-7 Hz) that can be directly measured and localized using MEG [1,2,4,36–39,62–64]. While TBI is not the only neurological disorder that generates abnormal slow-waves, in practice, brain tumor and stroke can be easily ruled out based on structural imaging (i.e., CT and MRI), whereas epilepsy, AD, and other chronic neurovascular diseases (e.g., hypertension and diabetes) can be ruled out based on medical history. Veterans with these confounding disorders will be excluded from this study. Using voxel-wise and ROI approaches, we demonstrated that MEG slow-wave source imaging detects abnormal slow-waves with ~85% sensitivity in patients with persistent PCS in chronic and sub-acute phases of mTBI [1,36]. MEG's high sensitivity for detecting mTBI allows us to study neuroimaging-based changes due to the passive neurofeedback treatment (i.e., IASIS) in Veterans with mTBI. This novel approach is scientifically and clinically significant since MEG slow-wave source imaging objectively measures functional changes in the brain due to the treatment, independent of the participants' subjective assessments of the treatment efficacy. The MEG findings can be used to further optimize the treatment strategy.

Automated voxel-wise MEG source-imaging for assessing mTBI on a single-subject basis: The present application will move MEG slow-wave source imaging forward as an effective clinical tool for assisting in mTBI diagnosis. One goal is to achieve high sensitivity of the proposed approach on a single-subject basis with high test-retest reliability and low false-positives. MEG slow-wave generations are expected to be heterogeneous, but unique to each individual patient, due to the nature of the injuries in mTBI (see Fig. 3). Individualized information can be used to design optimal treatment strategies targeting the abnormal brain areas on a singlesubject basis. Aim 1 uses our high-resolution MEG source imaging method, Fast-VESTAL [1,65], for mTBI diagnosis. The main innovative features are: 1) its high sensitivity and specificity for detecting abnormal slowwaves on a single-subject basis; 2) its voxel-wise approach, which provides a more evenly distributed positive detection rate over ROI approach; and 3) its automated procedure, which objectively localizes the abnormal slow-wave generators, and is independent of the data analyst's subjective judgments.

Fast-VESTAL: Localizing neuronal sources from abnormal MEG slow-waves poses great challenges to conventional MEG source-modeling techniques. Due to the nature of DAI and cholinergic abnormalities in mTBI, the actual number of neuronal sources generating abnormal MEG slow-waves can be large, and their time-courses can be correlated. The focal and multi-focal nature of the abnormal slow-wave generators during wakefulness [66,67] requires sparse-solution-based reconstruction techniques. We have developed a new high-resolution (sparse solution reconstruction), voxel-wise MEG source imaging technique, Fast-VESTAL [65]. Using simulations and human data, Fast-VESTAL's performance was assessed for its 1) ability to localize multiple correlated sources; 2) ability to faithfully recover source time-courses; 3) robustness to different SNRs including SNR with negative dB levels; 4) capability to handle correlated brain noise; and 5) statistical maps of MEG source images. An objective pre-whitening method was also developed in Fast-VESTAL to remove correlated brain noise [65].

B.3 Healing Mechanism of Slow-waves and Passive Neurofeedback Treatment for mTBI: IASIS a nd Nexalin:

The healing mechanism of slow-waves: Section B.2 explained that abnormal rs-MEG slow-wave during wakefulness can be used as an imaging marker for a sensitive detection of neuronal injury in mTBI. A more fundamental question is whether slow-wave generation is merely a negative consequence of neuronal injury or a signature of ongoing neuronal rearrangement / healing that occurs at the site of the injury. These two different views will lead to opposing mTBI treatment strategy designs. If the abnormal slow-wave generation is a negative consequence of the injury, the strategy should focus on cancelling the slow-waves during the treatment. On the other hand, if the slow-wave generation is part of a process of neuronal healing, the treatment should focus on potentiating endogenous slow-wave generation during the treatment. The literature on neural plasticity and stroke recovery supports the healing mechanism hypothesis of slow-waves [68,69]. Of course, for a successful treatment strategy, a desirable outcome should always be the ultimate elimination / substantial reduction of the abnormal slow-waves in mTBI by the end of the treatment course.

We favor the neuronal healing mechanism of slow-waves in mTBI. It has been shown that long-term potentiation induced in the motor cortex in humans, by means of intermittent theta burst stimulation, is

accompanied by a large and enduring increase of delta waves during wakefulness, suggesting a prominent role of delta waves in the neural plasticity processes taking place during the awake state [68]. Accordingly, the delta waves could be an epiphenomenon of cortical ongoing plasticity during wakefulness as during sleep and of the attempt of the cortex to reestablish a near-physiological functioning [68]. Furthermore, it was recently shown in an animal TBI study in rodents with DAI, that enhancing slow-wave sleep acutely after trauma by sleep modulation may have a beneficial disease-modifying effect in animals with acute TBI. The authors suggested that slow-waves in the delta-frequency range could be the key to functional improvement after TBI [70]. The mechanism of slow-wave-potentiated improvement could be linked with enhanced clearance of proteins and other waste products from interstitial space in brain [70]. Slow-wave sleep and anesthesia were associated with enhanced clearance of potentially neurotoxic waste products (e.g., -amyloid) in adult mice [71], whereas a correlation between -amyloid accumulation and disruption of non-REM sleep was observed in Alzheimer's disease patients [72], further supporting the potential benefits of enhanced slow-wave activity [70]. Therefore, we believe that the focus should be on technologies that potentiate endogenous slow-wave generation during mTBI treatment. To our knowledge, the proposed study will be the first to investigate whether potentiation of slow-waves in wakefulness has significant therapeutic benefits in treating chronic mTBI.

Overview of LIP-tES and IASIS: A promising class of treatments for mTBI is passive neurofeedback that applies low-intensity pulses using transcranial electrical stimulation (LIP-tES) with EEG monitoring. This class of EEG neurofeedback treatments use a common hardware design approved by the FDA (see FDA approval letter in Appendix), but different software/protocol approaches; examples include Low Energy Neurofeedback
System (LENS) [28], Flexyx Neurotherapy System (FNS) [29], and IASIS (the Greek word for healing or cure [30]. These treatments modulate brain-wave activity by applying LIP-tES using the same EEG cables and electrodes that measure the brain waves [32]. The electrical current associated with the low-intensity pulses delivered by these FDA approved devices is well-below the level of participant's perception and well-below the safety threshold. LENS and FNS have been used to treat individuals with TBI, including mTBI, showing positive effects on behavioral sequelae [31–35]. In addition, Larsen et al., reported that after neurofeedback treatment course, significantly decreased EEG amplitude was observed at the highest amplitude electrode site and at electrode Cz in a mixed population of individuals with TBI and other disorders [31].

IASIS technology potentiates endogenous brain oscillation: IASIS (Micro Current Neurofeedback) is typically a 6-week (two 30-minute sessions per week) passive neurofeedback intervention with EEG monitoring. The neural mechanisms underlying IASIS, and LIP-tES in general, are not completely understood [28]. LIP-tES belongs to a large category of transcranial electrical stimulation (tES) techniques that includes transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS) [73,74]. It has been proposed that anodal tDCS and tRNS increase neuronal excitability and may consequently enhance behavioral performance, that cathodal tDCS decreases neuronal excitability and subsequently worsens behavioral performance, and tACS increases neuronal excitability via entrainment of the desired neuronal firing frequency and consequently modulates performance [75]. However, this simplistic, sliding-scale reasoning (from excitation to inhibition or the reverse) does not always explain neurophysiological or behavioral outcomes [74]. Other models of tES mechanisms include the Stimulation-
Dependent, Activity-Dependent, Network Activity-Dependent, Excitation-Inhibition Balance, and Zero-Sum Models, each with its own strengths and limitations (see review in [74]). Recently, Fertonani and Miniussi proposed stochastic resonance (SR) as a useful mechanism to explain the general neuromodulation effects of tES [74]. SR is a phenomenon wherein an endogenous oscillatory brain signal, that is normally too weak to be detected, can be boosted by adding to the signal some noise or input that contains a wide spectrum of frequencies. We believe that the SR model may explain the treatment effects of LIP-tES, including IASIS, for mTBI. In IASIS, the low-intensity pulses contain a wide range of frequencies. When the repetition rate of these pulses is similar to the frequency of an underlying endogenous oscillatory brain signal, the SR effect may occur. Therefore, IASIS is a suitable technology for potentiating underlying endogenous brain rhythms including slowwaves, which makes it a good candidate for mTBI treatment.

Overview of Nexalin: Another promising treatment includes Nexalin brain stimulation. The Nexalin device, FDA clearance (501K=K024377, Classification: Stimulator, Cranial Electrotherapy: CFR 882. 5800: U.S. Patent #6904322B2), produces a waveform that provides tES to the brain delivered at a frequency of 4Hz, 40Hz, and 77.5 Hz at 0 to 15 mA peak current. There is evidence that this waveform, at this frequency, results in improved clinical outcomes in terms of anxiety and pain [114]. The specific mechanisms of action are not known, but available evidence suggests that this waveform alters the function of the hypothalamus and related structures. In particular, tES may lead to increases in levels of enkephalins and beta-endorphins in brain and CSF. Other data suggest that tES can alter

endogenous levels of both substance P and serotonin. Regardless of which neuropeptide or neurotransmitter is ultimately found to be modulated by tES, it is hypothesized that repeated TES treatments over time serve to stimulate long-term neurochemical changes.

B.4 Significance and Innovation: MEG Slow-wave Source Imaging for Assessing IASIS in mTBI

The present application takes an innovative approach to study the efficacy of IASIS treatment in mTBI, for the first time, using a double-blind placebo controlled design and rs-MEG slow-wave source imaging. We expect that IASIS will potentiate slow-wave generation and thereby potentiate the healing process. Previous LIP-tES studies have not linked treatment strategies to the potentiation of slow-waves during the course of treatment. Previous LIP-tES studies also have not used blinded (single- or double-blind) designs, so that behavioral outcomes may be contaminated by placebo effects. Moreover, functional or structural neuroimaging techniques have not been used to assess the effect of LIP-tES treatments on the brain in mTBI and their relationship to changes in behavioral outcomes. Thus, the mechanisms underlying potential benefits of treatment are poorly understood.

Our approach stands to considerably advance scientific and clinical knowledge about IASIS treatment for physical, cognitive, emotional and behavioral sequelae of TBI. We will test for the first time whether potentiation of slow-wave generation in wakefulness leads to significant therapeutic benefits in mTBI, including an ultimate reduction of abnormal slow-waves accompanied by an improvement in PCS and cognitive
functioning. Importantly, the proposed study will provide neuroimaging-based evidence for functional changes in the brain that underlie IASIS treatment effects in individuals with mTBI, independent of potential placebo effects. Information about the brain regions that generate abnormal MEG slow waves in each individual patient may also ultimately be used as a guide in developing optimal and subject-specific IASIS treatment protocols. We will also investigate the relationships among treatment-related changes in aberrant rs-MEG slow-wave generation and changes in PCS and neuropsychological measures, which may clarify specific behavioral sequelae that are more or less responsive to IASIS. High correlations between MEG slow-wave sources and clinical symptoms and/or cognitive dysfunction in mTBI patients will also significantly enhance the clinical relevance of MEG, advance its value for tracking the effects of recovery, and elucidate the source of post-mTBI cognitive deficits, which are controversial. Altogether, this study will substantially enhance our knowledge about the effect of transcranial electrical stimulation in mTBI mechanisms underlying LIP-tES, and its relevance to behavioral outcomes that significantly impact the quality of life in Veterans with mTBI.

B.5 Significance and Innovation: IASIS Effects on PTSD Symptoms

Veterans with mTBI often also have PTSD symptoms [25]. Many cross-sectional studies have found higher (nearly double) rates of PTSD in active-duty service members and Veterans with mTBI [27,76,77]. These findings have been corroborated using prospective study designs in civilians [78] and in two large active duty service members cohorts, the Marine Resiliency Study (MRS) and the Army Study to Assess Risk and
Resilience in Servicemembers (Army STARRS) [79,80]. Army STARRS reported a dose-response relationship between “very mild” (dazed but no loss of consciousness or amnesia), “mild” (some loss of consciousness oramnesia), and “more-than-mild” TBI and observed mental health outcomes, including PTSD [80]. These studies suggest that the extent of injury to the brain moderates the likelihood of the PTSD development. This view is consistent with a model in which TBI impairs functioning of prefrontal cortex that inhibits fear responses and promotes fear extinction [26,79]. Thus, we hypothesize that by treating mTBI using IASIS in Veterans with comorbid mTBI and PTSD, co-existing PTSD symptoms will also be reduced.

C. PRELIMINARY STUDIES

C.1 Voxel-wise Fast-VESTAL MEG Source

We have developed a high-resolution voxel-wise MEG source imaging techniquecalled Fast-VESTAL [65] (see B.2). In the present application, we propose to use Fast- VESTAL for localizing abnormal MEG slowwaves in Veterans with mTBI. The first step is to obtain voxel-wise MEG sources images in HC subjects, which will lead to the establishment of voxel-wise normative databases. Fig. 1 displays Fast-VESTAL MEG source images for the four frequency bands (data from 41 HC subjects) [65]. Source images were plotted using the t-test
between source magnitudes in HC subjects against empty room recordings when no subjects were in the MEG scanner. Despite resting-state alpha band (8 - 12 Hz) activity in humans being first detected by EEG [81] ~90 years ago and by MEG [82] ~50 years ago, Fig. 1 displays one of the first whole-brain voxel-wise MEG/EEG source images for resting-state signal (see [65] for details). Fig. 1 illustrates the feasibility of the voxel-wise MEG source imaging using Fast-VESTAL, and provides the foundation for establishing voxel-wise MEG normative HC database.

Figure 1 - See attached document.

C.2 Assessing the Positive Detection Rates of MEG Slow-wave Source Images in mTBI

We propose to study a voxel-wise MEG slow-wave source imaging approach for detecting mTBI on a single-subject basis. Fig. 2 shows Zcmax values (a measure of abnormal MEG slow-wave, see D. 3.2) obtained from voxel-wise MEG source magnitude source imaging, plotted separately for 1) 79 HC, 2) 36 blast mTBIs, and 3) 48 non-blast mTBIs [1]. There was minimal overlap of Zcmax values between each mTBI group and the HC group, with the patients in all mTBI groups showing markedly higher slow-wave Zcmax values than the HC subjects. These results provide the foundation for assessing abnormality of mTBI on a single-subject basis using MEG slowwave source imaging. With a 2.5 threshold (horizontal line in Fig. 2), the positive detection rates were 86.1% for the blast mTBI patients, and 83.3% for the non-blast mTBI patients. After combining blast and non-blast mTBI groups together, the positive detection rate was 84.5% [1]. No HC subjects showed a Zcmax value above the threshold (i.e., apparent specificity of 100%) which was chosen based on Youden index (see D.3.6). In contrast, the positive
detection rates using conventional MRI were 5.6%, 8.3%, and 7.1% for the same blast, non-blast, and combined mTBI groups, respectively. Based on the sensitivity defined in D.3.6, MEG slowwave source imaging was significantly more sensitive than MRI in detecting mTBI in the both blast and non-blast mTBI groups (McNemar test, $p< 10\text{-}6$) [1], which strongly supports Hypothesis 1. The limitations of this study were: 1) most of the HCs (i.e., 68 out of 79) were civilians without combat exposure, whereas all patients in the blast mTBI group had combat exposure, with 24 out of 36 blast mTBI patients active-duty service members and the remaining 12 Veterans; 2) cross-validation of the voxel-wise normative database was not performed. The present application will directly address these limitations in our normative database using HC Veterans with matching combat exposure. **Figure 2 - See attached document.**

C.3 Preliminary Data from Individual mTBI Cases using Single-subject-basis Analysis

Although the analysis using Zcmax provides crucial information for positive detection rate that may assist in diagnosis in a singlesubject basis, it does not address the loci and characteristics of abnormal slow-wave generation in individual mTBI patients. The voxel-wise framework based on Fast-VESTAL MEG source images identifies the sources of abnormal MEG slow-wave generation in individual mTBI patients. Fig. 3 shows the results of a single-subject-basis analysis that reveals statistically significant abnormal MEG slowwave generation (see D.3.5) from 8 representative mTBI cases in MNI space. The distribution of abnormal MEG slow-wave sources was in heterogeneous locations, but unique to individual mTBI patients, due to the nature of injuries. Such individualized information can be used to design optimal treatment strategies that target abnormal brain areas on a single-subject-basis. **Figure 3 - See attached document.**

C.4 Preliminary Data for Test-retest Reliability

Test-retest-reliability of single-subject MEG slow-wave imaging is an important component of the present application. In a pilot study, we
examined test-retest-reliability of MEG slow-wave source imaging for three chronic mTBI patients. In MNI space, Fig. 4 shows the abnormal
MEG slow-wave generations from two separate MEG exams in these patients. Very good test-retest-reliability was obtained, with the intra-class correlation coefficient (ICC) values of 75%, 81%, and 83% using the Zcmax, spatial correlation of spatial Z-score maps, and coordinates of the centers-of-mass, respectively (see D.3.7 for details). These preliminary results support Hypothesis 1. **Figure 4 - See attached document.**

C.5 IASIS Potentiates Endogenous Slowwaves Immediately after a Treatment Session

Fig. 5 shows preliminary data from a HC subject who participated in one session of IASIS. Three MEG exams were performed: the first right-before IASIS, the second immediately after IASIS (i.e., within a few minutes), and the third 96 hours after IASIS, all during wakefulness. The left panel of Fig. 5 shows a typical train of IASIS pulses at 3.6 Hz repetition rate (see Section D.4.1). The right panel shows that no abnormal MEG slow-waves (delta-wave band) were detected in either the MEG exam before IASIS and 96 hours after, which would be expected for a HC subject. However, immediately after IASIS, above threshold MEG slow-waves were detected from mid-line precuneous, mid-line vmPFC, bilateral medial temporal near hippocampus and amygdala, left insular, and cerebellum. These areas closely match the known brain networks observed during delta-wave sleep [83,84]. Due to strong artifacts from the IASIS device (left panel), we cannot obtain meaningful MEG slow-wave images during the IASIS session. However, we believe that the potentiation of slow-waves started during the IASIS session.
These preliminary data suggest that immediately after an IASIS treatment session, MEG slow-waves are potentiated in the same brain networks of delta-wave sleep, which supports Aim 1 and Hypothesis 2. **Figure 5 - See attached document.**

C.6 Ultimate Reduction of PCS and Abnormal MEG Slow-waves Post IASIS Treatment Course in mTBI

We performed a pilot study to assess the ultimate changes in MEG slow-waves and PCS in 6 individuals with chronic mTBI who went through the IASIS treatment course. IASIS treatments were applied twice weekly for 6 weeks, with MEG exams and PCS assessments at baseline and follow-up. None of the indiviudals from this pilot study had adverse events or noted side-effects.

C.6.1. Ultimate pre- and post-IASIS changes in PCS and PCL scores: We found significant reductions of PCS in all 6 mTBI individuals. RPQ total scores across 16 categories were significantly reduced after the IASIS treatment (Fig. 6A) (paired group ttest, t=5.80, p< 0.01, Cohen's d=2.37). Significant reduction was also found in the Sleep Disturbance sub-category of the RPQ (paired group t-test, t=3. 00, p< 0.05, Cohen's d=1.22). These preliminary results provide strong support for Aim 2 and Hypothesis 4. We also collected PCL scores in 4 out of the 6 participants. Compared with pre-IASIS PCL, there was a trend of reduction in Post- IASIS PCL score (paired group t-test, t=1.90, p=0.15, Cohen's d=0.95), which also supports Hypothesis 5.

C.6.2. Ultimate pre- and post-IASIS changes in total abnormal MEG slow-wave generation: Fig. 6B shows a striking reduction in total abnormal Z-scores (see D.4.3) that measured abnormal MEG slow-wave generation between the pre- and post-IASIS MEG exams. The change in total abnormal MEG Z-scores was significant (paired group t-test, t=4.28, p< 0.01, Cohen's d=1.75). This preliminary result shows that IASIS ultimately reduced abnormal MEG slow-waves in these individuals. This finding supports Aim 1 and Hypothesis 3. Next, we correlated the change (i.e., (pre - post) / pre) in MEG slow-waves due to treatment with relative change in the total RPQ scores. Relative total abnormal MEG Z-score change significantly correlated with relative total RPQ score change (r=0.84, p< 0.05, Fig. 6C). This finding supports Aim 3 and Hypothesis 6.

C.6.3. Ultimate pre- and Post-IASIS changes in PCS and MEG slow-wave imaging for individual participants: Here, detailed information is provided for individual participants. Fig. 7 shows the loci of abnormal MEG slow-waves pre- and post-IASIS treatment in each of the 6 mTBI participants. Participant #1: After IASIS, Participant #1's overall RPQ score went down from 46 to 25, a reduction of 45.7%. His PCL also went down from 57 to 44, a reduction of 22.8%. Compared with pre-IASIS MEG, his post- IASIS MEG showed marked reduction of 68.6% in total abnormal MEG Z-score. Markedly reduced abnormal slow-waves were found in frontal pole, posterior cingulate cortex (PCC), right insula, and right hippocampus (Fig. 7). The MEG findings were compatible with reduced PCS for headaches (posterior insular), memory function (related to hippocampus), and feelings of frustration or impatience (frontal pole). Participant #2: After IASIS, Participant #2 reported a reduction in overall RPQ score from 54 to 27 (i.e., by 50.0%). PCL was not available. There was a 45.1% reduction in her total abnormal MEG Z-score after IASIS relative to the baseline MEG exam. Markedly reduced MEG slow-waves were found in anterior cingulate cortex (ACC), right lateral occipital cortex, and right occipital fusiform gyrus (Fig. 7). The MEG findings were also compatible with reduced PCS for headaches (ACC) and photophobia (occipital cortex and fusiform gyrus). Participant #3: After IASIS, Participant #3's total RPQ score drastically reduced from 31 to 15, a reduction of 51.6%. His PCL also went down from 6 to 5, a reduction of 16.7%. Compared with the pre-IASIS exam, his post-IASIS MEG exam showed a 45.8% reduction in total abnormal MEG Z-score. Markedly reduced abnormal slow-waves were found in PCC, bilateral orbital frontal cortex (OFC), and left hippocampus (Fig. 7). The MEG findings are compatible with reduced PCS for memory problems (hippocampus) and headaches (PCC). Participant #4: After IASIS sessions, this participant's overall RPQ score dropped drastically from 14 to 1, a reduction of 92.9%. His PCL also went down from 31 to 2, a 90.3% reduction. The pre- and post-IASIS MEG exams show a 74.2% reduction in total abnormal MEG Z-score. Marked reductions of abnormal slow-waves were found in the right inferior-lateral parietal area/superior temporal gyrus (STG), right hippocampus and amygdala, right inferior temporal pole, and left cerebellum (Fig. 7). The MEG findings were compatible with reduced PCS for noise sensitivity (STG) and forgetfulness (hippocampus and inferior temporal area). Participant #5 only finished 4 out of the 12 required IASIS treatment sessions. His RPQ total score changed from 51 to 45, with only a marginal reduction of 11.8%. PCL was not available. In his MEG exam following the 4th IASIS treatment visit, his total abnormal MEG Z-score only showed only a marginal reduction of 12.0%. Abnormal slow-wave generation from the right ACC and PCC remained essentially the same. Reduced slow-waves were observed from his right striatum / insular cortex and his right parahippocampus, but increased slow-wave generation was found from his left vmPFC (Fig. 7). The MEG findings were compatible with his persistent PCS at his 4th visit for headache (ACC and PCC) and irritability (vmPFC). Participant #6's total RPQ score reduced from 31 to 11, a marked reduction of 64.5% after IASIS treatment. His PCL went down from 27 to 23, a 14.8% reduction. The pre- and post-IASIS MEG exams show that he had a 76.1% reduction in total abnormal MEG Z-score. Marked reductions of abnormal slow-wave generation were found in the right auditory cortex, superior temporal gyrus, as well as right supplementary motor area (SMA) and ACC (Fig. 7). The MEG findings were compatible with reduced PCS for noise sensitivity (auditory cortex in superior temporal gyrus), as well as headaches and poor concentration (SMA and ACC). **Figure 6 and 7 - See attached document.**

C.7 MEG Correlated with PCS Scores and Neuropsychological Scores in mTBI

MEG slow-wave correlates with PCS score in mTBI: Voxel-wise correlational analyses of MEG slow-wave measures and PCS were performed in the blast and non-blast mTBI groups described in C.2. Significant positive correlations were found between MEG source magnitude and PCS scores (Fig. 8, r>0.55) [1]. In the blast mTBI group, personality symptoms (e.g., social problems) correlated with MEG slow-waves in bilateral OFC and medial PFC; trouble concentrating and affective lability both correlated with slow-waves in left OFC; blurred vision/visual difficulties correlated with slow-waves in right fusiform gurus. In the nonblast mTBI group, depression symptoms correlated with slowwaves in ACC. In combined blast and non-blast mTBI groups, only MEG source magnitude from right OFC correlated with trouble concentrating (not shown). The threshold of the voxel-wise analyses was at q=0.05 by FDR [85]. These results support Hypothesis 6. MEG slow-wave correlates with neuropsychological scores in 31 mTBI patients: Fig. 9 shows brain regions with negative correlations (|r| > .45) between rs-MEG slowwave magnitude and performance on DKEFS Color Word Interference test. Specifically, poorer inhibitory control was associated with higher rs-MEG slow-wave magnitude in the right dlPFC, bilateral supramargional gyri, ACC, right hippocampus, and left inferior temporal lobe. These results also support Hypothesis 6. **Figure 8 and 9 - See attached document.**

C.8. Preliminary Data for Nexalin

The pulse-based tES (as administered by the Nexalin apparatus) is a way to alter brain functions with low intensity electrical current undetectable by the participants. . A prior randomized, controlled trial compared antidepressant medication with Sham TES, Placebo with Nexalin at a lower dose, and Placebo medication with Nexalin at a higher dose. All three conditions showed remission of depressed mood by the end of treatment and maintenance of remission status following 12 weeks of follow-up. Thus, the effect sizes for Nexalin treatment were comparable to antidepressant medication. It should also be noted that the Nexalin device has undergone extensive safety analysis indicating that the device is safe for its intended use. Additionally, the classification of the device places it into a nonsignificant risk (low risk device) category. A review of Phase III Pivotal Clinical Trials (with a follow up period of one year) demonstrates that Nexalin TES Therapy does not result in any significant adverse events or side effects. In fact, there was no significant difference between reported events in the placebo group and reported events in the active treatment group.

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.

D. RESEARCH DESIGN AND METHODS

D.1 Human Subject Recruitment, Clinical Symptoms, Neuropsychological Exams

D.1.1. Human subject recruitment and flow chart:

This study will assess traumatic brain injury among Veterans using either blast-related and non-blast related criteria. The research results will be generalizable to the Veteran population who also incur head injuries from sports, falls, or motor vehicle crashes.

We propose to study a total of 175 subjects in three groups. Two groups contain OEF/OIF/OND Veterans (age 18-60) diagnosed with chronic mTBI with persistent PCS (majority due to blast). Participants in these two groups will be matched on age, gender, education, combat exposure, symptom chronicity, and socioeconomics. Group 1 (mTBI-IASIS group, N=50) contains mTBI Veterans to be blindly assigned to a 6-weeks IASIS treatment with two sessions per week. Group 2 (mTBI sham group, N=50) contains mTBI Veterans to be blindly assigned to a sham treatment for 6 weeks with also two sessions per week. Veterans with mTBI in both Groups 1 and 2 must currently have persistent PCS at least 6 months post injury (i.e., the most recent injury). In addition, PTSD symptoms will be assessed and matched in symptom severity and diagnostic category in the two mTBI groups. Group 3 (control group, N=75): age-, gender-, education-, combat exposure-, and socioeconomically-matched HC Veterans.

The above table and Fig. 10 shows the study flow chart with 16 visits. After consent, Visit 1 for all three groups will include baseline neuropsychological (NP) and mental health assessment (MHA). Then, baseline rs- MEG and MRI scans will be performed in Visit 2 for all participants. The rs-MEG data from the HC group will be used to establish a normative HC database. Next, a re-test rs-MEG exam will be performed in a subset of HC participants (N=25, green dashed line) at Visit

3 in order to confirm the test-retest-reliability of the normative database. In contrast, at Visit 3 the mTBI participants in IASIS and sham groups will undergo a pre-session MEG, the first IASIS /Sham treatment session (S1), and a post-session MEG exam. The pre-session MEG in Visit 3 can be used as a re-test exam with respect to the Visit 2 baseline MEG for analyzing test-retest-reliability in the mTBI groups. In addition, the same pre-session MEG exam in Visit 3 will be compared with Visit 3 post-session MEG to assess possible potentiation of slow-waves due to the IASIS session (or lack of potentiation in the sham session). Next, the mTBI participants continue their IASIS/Sham treatment sessions (S2-S6) in visits 4-8. During the mid-treatment Visit 9, another pair of pre- and post-session MEG exams and NP will be performed. The mTBI participants will continue treatment sessions (S8-S11) in Visits 10-13. During the final treatment Visit 14, the third pair of pre- and post-session MEG exams will be performed. One week after the participants finish their final IASIS/Sham treatment session (S12), a one-week follow-up MEG and NP exams will be conducted during Visit 15. Finally, a subset of IASIS group (N=25) will be tested one month after the final treatment for a one-month follow-up MEG. To reduce drop-out rate, participants initially in the mTBI-sham group will also be offered the real IASIS treatment, but no MEG or behavioral data will be collected for that treatment. **Figure 10 - See attached document.** If, after IASIS treatment is complete and participants in the mTBI group may have remaining PCS, additional Nexalin treatment will be offered.

D.1.2. Exclusion criteria for study participations include: 1) history of other neurological, developmental, or psychiatric disorders (based on the DSM-5 (MINI-7) [86] structured interview), e.g., brain tumor, stroke, epilepsy, Alzheimer's disease, schizophrenia, bipolar disorder, ADHD, or other chronic neurovascular diseases such as hypertension and diabetes; 2) substance or alcohol use disorders according to DSM-5 [87] criteria within the six months prior to the study; 3) history of metabolic or other diseases known to affect the central nervous system (see [88] for similar criteria); 4) Metal objects (e.g., shrapnel or metal fragments) that fail MRI screening, or extensive metal dental hardware (e.g., braces and large metal dentures; fillings are acceptable) or other metal objects in the head, neck, or face areas that cause non-removable artifacts in the MEG data; 5)

Potential subjects will be administered the Beck Depression Inventory (BDI-II) to evaluate level of depressive symptoms, and suicidal ideation; any participant who reports a "2" or "3" on the BDI–II: item 9 (suicidal thoughts or wishes) will also be excluded. However, depression following mTBI or traumatic event of PTSD is common [89]; therefore, in two mTBI groups, we will include and match patients with depression symptoms reported after their injury/event, and will co-vary BDI-II score in data analyses.

D.1.3. Inclusion for the mTBI groups: All symptomatic mTBI patients will be evaluated in a clinical interview to document the nature of the injuries and ongoing PCS. The diagnosis of mTBI patients is based on standard VA/DOD diagnostic criteria. Inclusion in the mTBI patient group requires a TBI that meets the following criteria: 1) a loss of consciousness (LOC) < 30 minutes or transient confusion, disorientation, or

impaired consciousness immediately after the trauma; 2) post-traumatic amnesia (PTA) < 24 hours; 3) an initial Glasgow Coma Scale (GCS) [90] between 13-15 (if available). Since the GCS assessment is often not available in theater, Veterans with missing GCS, but who meet other inclusion criteria will also be recruited. Each patient must have at least 3 items of persistent PCS (see below) at the beginning of the study.

D.1.4. Inclusion of HC group: Participants that qualify as HCs will be age, education, combat exposure, and socioeconomically matched to the mTBI groups. In addition to exclusion criteria listed above, HC subjects must not have been diagnosed with head injury, affective disorder, or PTSD (CAPS-5 < 8) throughout life.

D.1.5. Assessing persistent PCS scores in mTBI: Ongoing PCS in mTBI will be assessed utilizing the Neurobehavioral Symptom Inventory (NSI) [91] and Rivermead Post-concussion Symptom Questionnaire (RPQ) [20]. NSI is a PCS questionnaire widely used in Veterans [91]. The NSI was devised to gauge the severity of PCS and track symptoms over time, and is a 22 item self-report questionnaire that assesses severity of cognitive, somatic, and emotional symptoms. The severity of PCS is measured using a Likert scale ranging from 0 (not experiencing) to 4 (a very severe problem), thus, NSI allows for a correlational analysis between symptom severity and MEG findings. While the NSI is able to track PCS symptoms over the last 2 weeks, we will also assess the PCS using the RPQ [20], a 16-category questionnaire that addresses PCS symptoms over the last 24 hours. As we will be performing multiple IASIS sessions, this 24 hour scale is required. For Veterans with blast mTBI, we will also collect information about secondary and tertiary injuries. At baseline, we will assess combat exposure using the Combat and Post-battle Experiences Scales of the

Deployed Risk and Resilience Inventory 2 (DRRI-2) [6], which takes into account the amount level of combat and post-battle exposures, and this coupled with a clinical interview that will detail the amount of times each participant has been exposed to a possible subconcussive blast. In patients with multiple mTBIs, a history of the most recent and all prior mTBIs (life-long) will also be documented for analyzing the effects of repetitive mTBI on MEG slow-wave source imaging. In patients with multiple TBIs, both old and new injuries may contribute to the generation of abnormal MEG slow-waves. Lifetime history of TBI will be assessed using the Ohio State University Traumatic Brain injury Identification method (OSU TBI-ID) [19]. Since sleep is

often disrupted in mTBI, the Pittsburgh Sleep Quality Index (PSQI) [17] will be given to assess for 7 different components of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction over the last month. The McGill Pain Questionnaire (MGPQ) [18] will evaluate the level of current pain, pain changes over time, and strength of pain, since pain is frequently co-morbid with mTBI. In addition, the order of mTBI to PTSD will be collected.

D.1.6. Assessing mental health PTSD symptoms: At Visit 1, participants in all three groups will be evaluated by a psychologist or research associate under the supervision of Co-I, Dr. Baker, using a structured clinical interview, the Mini- International Neuropsychiatric Interview (MINI-7) [86] to rule in/out mental health disorders, and the Clinician- Administered PTSD Scale (CAPS-5) [7] for DSM-5 [87]. The CAPS-5 is a standard semi-structured interview used to assess PTSD diagnosis and severity. As part of as a structured interview, the primary traumatic event is elicited and will be used as the basis of assessing PTSD symptoms. The CAPS-5 total symptom severity score is calculated by summing severity scores for the DSM-5 PTSD symptoms that are assessed with this 30 item questionnaire. PTSD diagnostic status will be assessed using the past month version of the CAPS-5. The CAPS-5 has the advantages of categorical (diagnostic) or dimensional scoring of PTSD plus items for assessing social and occupational functioning, dissociation, and the validity of the items. A total severity score of 33 or higher indicates full threshold PTSD [7]. The CAPS-5 past week version quantitative data will be given prior to treatment and at follow-up (Visit 15) and used for evaluation of treatment (IASIS or sham) and for correlation with MEG data. PCL-5 [8] will also be given in Visits 1 and 15 to track changes in PTSD symptoms.

D.1.7. Alcohol, smoking, substance uses: We will utilize Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) [15] to assess alcohol and substance use over the lifetime and frequency of past 3 months. Alcohol Use Disorders Identification Test (AUDIT) [16] will assess alcohol abuse problems.

D.1.8. Medications known to affect MEG: Participants will continue on their current medications. All medications taken by each participant will be noted during a pre-consent screening process, followed by another full screening during consent, in case of medication changes. Each medication is documented for its specific drug class and compared to the published information that documents the effects of specific drug(s) on EEG or MEG delta frequency band [66]. A small class of medications (e.g., some sedative neuroleptics) are known to increase EEG and MEG delta-band power [66]. The IASIS treatment will not interfere with the participant's ongoing treatment. If the participant is currently undergoing Cognitive Behavioral Therapy or Medication Treatment, they will still be enrolled in the study as this is an appropriate representation of the population. All participants will be allowed to be on their currently prescribed medications, but will be asked to remain on the same medication regimen during the course of the IASIS treatment. The participants enrolled must have been stable in their current medications for at least 6 weeks. Since we will focus on changes in MEG due to IASIS, allowing participants to remain on current medications should not affect the results.

D.1.9. Neuropsychological Exams will be performed to assess cognitive dysfunction and its correlation with abnormal MEG measures. Complete test batteries pre- and post-treatment will assess domains of cognition that have differentiated mTBI and HC in previous research [92,93] using measures previously validated for TBI [94]. These domains include verbal learning and retrospective memory (California Verbal Learning Test-2nd Edition) [92]; processing speed (Symbol Search and Coding subtests from the Wechsler Adult Intelligence Scale-4th Edition (WAIS-IV; [95]); executive function (Verbal Fluency, Trail-Making and Color- Word Interference subtests from the Delis-Kaplan Executive Function System [96]); and attention/working memory (WAIS-IV Digit Span subtest). Because preliminary analyses of our previous cohort showed that self reported symptoms of traumatic stress significantly correlated with impulsive responding on The Connors Continuous Performance Task II (CPT-II) [97], it will be included as a measure of attention and impulsivity. Impulsivity will also be measured by Barratt Impulsivity Scale [98], a self-report questionnaire. Since frontal lobe areas are more prone to damage, the Frontal Systems Behavior Scale [99] will measure behavioral dysfunction associated with frontal subcortical impairment. The Wechsler Test of Adult Reading [100] will provide an estimate of premorbid ability. Effort will be assessed using the Test of Memory Malingering (TOMM) [9]. Alternate forms of tests will be used post-treatment when available. As we require participants to adequately rate their symptoms during their treatment sessions, we would require that the symptom validity tests (SVT) measures be passed. If the participant fails the SVT measures, such as the TOMM, he/she will be removed from the study. In order to measure change at multiple time points, we will administer the Detection, Identification, and Two-back tests from CogState Ltd, a tablet-administered battery optimized with multiple versions for use in clinical trials. These will be administered pretreatment (Visit 1), at the treatment mid-point (Visit 9), and post-treatment (Visit 15).

D.2 Data Acquisition for MEG and MRI

MEG data acquisition: rs-MEG data will be measured in alert condition using our Elekta-Neuromag VectorView MEG system. The entire recording will have three 5-minute blocks with eyes closed and a 60 sec break with eyes-open between each block. The participant will be instructed to keep the eyes closed and empty his/her mind while staying alert (see [1]). Data will be sampled at 1000 Hz. Eye blinks, eye movements, and

heart signals will be monitored. Three minutes of empty-room data will also be acquired to assess the sensor and environment noises. Precautions are taken to ensure head stability and minimize head movements (< 3 mm) (see [1]). We focus on eyes-closed rs-MEG data since low-magnitude eye-related artifacts can be easily removed, whereas eyes-open rs-MEG data are often contaminated by eye-blinks and strong eye-movement artifacts that cannot be fully removed without substantially diminishing the brain signals.
Conventional MRI and the construction of the BEM: Using a 3T GE Discovery MR750 MRI scanner, we will acquire a high-resolution MRI volume with a resolution of 1 1 1 mm3 using a T1-weighted 3D-IRSPGR pulse sequence. Gradient nonlinearity spatial distortion in MRI will be corrected using software developed by our collaborator, Dr. Ander Dale's lab [22]. The T1-weighted images will be used to construct a source grid for Fast VESTAL and a boundary element method (BEM) model for MEG forward calculation [101]. BEM mesh is onstructed by tessellating the inner skull surface from the T1-weighted MRI into ~6000 triangular elements with ~5 mm size. Cubic source grid with 5 mm size and ~10,000 nodes covering the whole brain is used to calculate the MEG gain (i. e., lead-field) matrix. Conventional MRI sequences for identifying mTBI lesions in
Veterans will also be performed: 1) Oblique T2*-weighted; 2) Oblique T2-weighted with ASSET; 3) Oblique FLAIR; 4) Oblique DWI. Susceptibility-weighted imaging will also be performed to detect subtle blood products.

D.3 Detecting mTBI using Voxel-wise MEG Slow-wave Source Imaging and Conventional MRI (Aim 1)

D.3.1. MEG source imaging procedure for slow-waves: Eyes-closed rs-MEG data is first run through MaxFilter [102] to remove external interferences (e.g., artifacts due to metal objects, strong cardiac signals, environment noises, etc.), and to correct head movement. Next, residual artifacts due to micro eye-blinks, eye movements, and residual cardiac signals are removed using Independent Component Analysis using ICALAB
(Riken, Japan). Here, the 2nd and 3rd 5-minute rs-MEG sensor-waveform datasets are registered to the 1st 5- minute dataset using MaxFilter. The artifact-free, eyes-closed, rs-MEG sensor-waveform datasets are divided into 2.5 second epochs. The data in each epoch are first DC-corrected and then run through a 1-4 Hz bandpass filter. Sensor-waveform covariance matrices are calculated for individual epochs after the band-pass
filtering; then, the final sensor-waveform covariance matrix is obtained by averaging the covariance matricesacross individual epochs for the total 15-minute data. Using such a covariance matrix, voxel-wise MEG slowwave source magnitude images are obtained for each participant following the Fast-VESTAL procedure [65].
D.3.2. Establishing voxel-wise normative database for MEG slow-wave source magnitude imaging: We will develop a voxel-wise whole brain MEG source imaging approach for detecting abnormal MEG slow-waves in mTBI participants. The specific steps will be: 1) the brain volume of each subject is divided into a MEG source grid with uniform grid size in x, y, and z directions using the 3D T1-weighted MRI. Fast-VESTAL source
magnitude imaging will be obtained on this source grid for the 1-4 Hz frequency band [1,65]. 2) The Fast-VESTAL source magnitudes will undergo a logarithm transformation and be registered to the standard MNI-152 brain atlas using linear (FLIRT) / non-linear (FNIRT) registration methods from FSL (Oxford, UK) with spatial smoothing using a Gaussian kernel of pre-defined full width half maximum (FWHM). 3) Repeat Steps 1-2 for all HC subjects and a voxel-wise normative MEG slow-wave database will be established. Fractional polynomials will be used to model the effects of variables like age, gender, combat exposure, and education. The fitting parameters for these variables will be saved for each voxel, as part of the normative database. After adjusting for these variables, mean values and standard deviations (SD) will be calculated for each voxel to form the key features of the normative database. 4) The Kolmogorov–Smirnov (K-S) test will be used to assess if the database is Gaussian distributed. A "normative mask" containing all voxels that survived the K-S Gaussian distribution tests will be created for the normative database. 5) For each HC subject, the MEG source magnitude images are first run through the normative mask and processed to adjust for the age, gender, combat exposure, and education variable, using the previously saved fitting parameters from normative database. 6) The source magnitude images are then converted into voxel-wise Z-score images using the mean values and SDs from the normative database. 7) A standard cluster analysis is performed for each Z-score imaging volume to control for family-wise errors, using the new version (after May 2015) "3dFWHMx" and "3dClustSim" functions in AFNI. The thresholding cluster-size (Rc) is provided by "3dClustSim" for a corrected p=0.01 in the analysis. 8) For each voxel, a cluster-wise Z-score (Zc) which is the mean value of Z-score across all neighboring voxels within Rc will be calculated. The maximum value of the cluster-wise Z-score (Zcmax) across the whole brain volume is obtained for each subject. The smoothing factor in Step 2 is chosen to minimize the cross-validated mean square error of prediction.
D.3.3. Tasks to evaluate the normative database: We will examine the properties of the HC normative database: 1) to study the database's behavior for deep sub-cortical versus cortical areas; 2) to identify the voxels in the database that meet the requirement of a Gaussian distribution; 3) to test the database's sensitivity to spatial smoothing factors; 4) to assess the database's false-positive rate (i.e., specificity exam) by testing MEG data using the k-fold

validation test (see below); 5) to study a non-parametric approach based on bootstrapping, to expand our approach to voxels that do not meet the Gaussian distribution; 6) to examine the test-retest reliability of the normative database using repeated measures from a subset (N=25) HC Veterans.

D.3.4. Determining the optimal threshold for Zcmax or other MEG measures, and assessing the specificity (true-negative rate) of MEG slow-wave source imaging: We will examine a variety of thresholds for Zcmax or other MEG measures: 1) For each threshold value, we will assess the specificity of Zcmax or other MEG measures using the k-fold cross-validation method. The k results from the folds can then be averaged (or otherwise combined) to produce a single estimation. 2) For each threshold value, we will assess the number of TBI subjects showing above threshold MEG slow-waves in terms of Zcmax or other MEG measures. Optimal threshold for sensitivity-specificity will be determined using the Youden's index [103] and/or the ROC curves.

D.3.5. Detecting single-subject-basis abnormal MEG slow-waves in mTBI: In mTBI groups, we will apply a voxel-wise approach to identify areas with abnormal MEG slow-wave on a single-subject basis [1]. First, the rs- MEG data in each patient will be processed following the same above Steps 1-2, 5-6, and 8 in D.3.2. Sensitivity assessment of Zc in individual Veterans will be performed in mTBI groups to identify the loci that generate abnormal slow-waves [1] (Fig. 3). The positive detection rate of MEG slow-wave source imaging will be assessed using the Zcmax (see Fig. 2). Since the brain areas injured by TBI are highly heterogeneous across individuals, and often without a global effect, using the Zcmax value across the whole brain is equivalent to examining the hypothesis that at least one region shows abnormal slow-waves.

D.3.6. Assessing the sensitivity and specificity values in mTBI: conventional MRI versus MEG slow-wave: MRIs will be reviewed by a Board certified neuroradiologist (Dr. Lee) to determine if the participants have visible lesions. An MRI diagnostic variable of sensitivity (positive detection rate) will be created with “Y” for participants in mTBI and HC groups showing abnormal MRI finding(s) and “N” for the ones with normal results. Participants with visible ventricular dilation or ventricular asymmetry will be excluded from the HC group. T2-weight hyperintensities may or may not be associated with mTBI. Incidental age-related T2-wetighted hyperintensities may show in some healthy participants without any association with head injury. Therefore, only Veterans with beyond age-appropriate T2-weighted hyperintensities will be considered positive in the HC group. In mTBI groups, participants with visible lesions, ventricular dilation, ventricular asymmetry, or beyond age-appropriate T2-weighted hyperintensities will be considered as positive MRI findings. In our experience, only in rare cases do HC subjects show some beyond age-appropriate hyperintensities in T2-weighted MRI. Otherwise, MRI in HC group will be negative. Therefore, the MRI specificity will be greater than 90%.

We will also assess the sensitivity and specificity of MEG using the Zcmax measures (see preliminary data in C.2). MEG sensitivity and specificity variables are defined in the same way as for MRI. The standard Youden's index [103] will be used to calculate the optimal cut-off value (threshold of Zcmax) [104] (see embed in Fig. 2). The nominal MEG sensitivity and specificity variables based on the Youden's index will be obtained with “Y” for abnormal and “N” for normal. McNemar’s test, the non-parametric equivalent of the t-test for dependent means in nominal data with two observations, will be used to assess the statistical difference in sensitivity of MEG source imaging relative to conventional MRI. We will select the cut-off value such that the MEG specificity is at least 90% when comparing the sensitivity values between MEG and MRI for diagnosing mTBI. We expect high sensitivity and specificity in MEG slow-wave imaging for detecting mTBI (Hypothesis 1). D.3.7. Assessing the test-retest reliability of voxel-wise MEG slow-wave imaging: We will have two consecutive MEG exams for participants in 50% of the HC group, and 100% in the two mTBI groups at Visits 2 and 3 (Fig. 10). Test-retest reliability will be assessed by the intra-class correlation coefficient (ICC), which estimates the proportion of between-subject variance to total variance. ICCs between 0.75 and 1.0 are considered "excellent" [21]. Conservative ICC 0.75 will be adopted in Hypothesis 1. We will examine testretest reliability for three MEG source imaging measures: 1) Zcmax; 2) spatial correlation between the spatial Zscore maps of MEG source images; 3) spatial distances between the centers-of-mass for each cluster of voxels that showed positive slow-waves (only in mTBI groups); 4) voxel cluster sizes; and 5) measures of central tendency and variability. We will also study the test-retest reliability using Cronbach’s alpha-internal consistency table. Our preliminary results demonstrates high ICCs for MEG source imaging (C.4, Fig. 4).

D.3.8. Refinement of Fast-VESTAL and analyzing MEG data using conventional methods: L1-minimum types of solutions, including Fast-VESTAL, provide sparse solutions. It was shown that the high degree of spatial smoothing has an adverse effect on the positive detection rate of mTBI [1], which suggests that MEG source imaging methods with high spatial resolution (being sparse) may have unique advantages for mTBI. To systematically examine this topic, we will also analyze the MEG same data using conventional MEG source imaging techniques such as L2-minimum norm (MNE [105] and sLORETA [106] with non-sparse solutions), beamformer [107], conventional dipole fitting [38,39], as well as Champagne [108]). We will also refine Fast-VESTAL and further test its performance for 1) non-focal sources and 2) for deep sub-cortical sources.

D.4 Assessing Efficacy of IASIS Treatment using MEG Source Imaging in Veterans with mTBI (Aim 1)

D.4.1. IASIS Procedure: IASIS (Micro Current Neurofeedback [30]) is a 6-week (two 30-minute sessions per week) passive neurofeedback LIP-tES intervention with EEG monitoring. The IASIS device uses 5 EEG electrodes. The EEG interface device is the J&J Engineering I-330 C2, provided specifically for IASIS. The EEG sampling frequency is 256 Hz on each of 2 EEG acquisition channels. The feedback LIP-tES is delivered
via the 4 EEG leads (A+, A-, B+, B-), with respect to the Common Neck Reference (isolated). During each session, 2 electrodes (A- and B-) are attached to the participant's left and right mastoids, while the remaining two electrodes (A+ and B+) are moved to various locations on the scalp to record EEG signals. All four (A+, A-, B+, B-) electrodes are involved in applying weak electric current pulses back to the brain (the feedback
process). The feedback signal consists two types of narrow pulse trains, both with 150 mV in amplitude: A Type 1 pulse is 25 ms in duration and contains carrier waves at ~50 KHz. The repetition rate of Type 1 pulse train is fixed at 3.6 Hz (Fig. 5); A Type 2 pulse is 120 ns in duration and contains carrier waves at ~100 MHz. The repetition rate of Type 2 pulse train is in 2 Hz - 12.5 Hz range and determined dynamically by adding
incremental frequencies specified in pre-programmed schedules to the dominant brainwave frequency (from EEG recordings). For example, IASIS first picks up the dominant brain rhythms (e.g., 3 Hz). Next, the feedback electrical pulses are sent back to the brain, with a repetition rate by adding incremental frequencies (e.g., 1 Hz, 2 Hz, etc.) to the dominant one, changing each 5 seconds throughout the 25-second-long protocol. According to the SR model, these feedback pulses potentiate endogenous slow-waves in the brain. A train of IASIS pulses with specific repetition rate will not only potentiate oscillation at that frequency, but also oscillations with lower frequencies. This process is similar to studies that used trains of electrical / magnetic pulses to potentiate oscillations at lower frequency than the pulse-train's repetition rate in animals and humans [68,109].

Moving A+ and B+ electrodes to various places may draw unnecessary attention from the participant to specific electrode sites. To avoid that, we prep and pre-place a set of electrodes on the scalp of the participant following the 10-20 EEG configuration. These 10-20 sites are the potential sites for the A+ and B+ electrodes. During the treatment sessions, the sites of A+ and B+ electrodes (selected from the pre-placed 10-20 configuration) will be switched by software without the participant's knowledge, so that the participant cannot tell which sites were activated. Out of the standard 10-20 electrode sites, electrode pairs activated were: F3/F4, C3/C4, P3/P4, O1/O2, T5/T6, Fz/Pz, FPz/Cz, FP1/FP2, F9/F10, F9/FC3. Each Schedule takes between 22-25 seconds per site and each Schedule is delivered twice per electrode pair.

D.4.2. Sham treatment and double-blind design: During the sham treatment, we will still prep and preplace the electrodes for common reference, A-, B-, plus the set of electrodes on the scalp of the participant following the 10-20 EEG configuration for A+ and A-, just like the procedure for real IASIS treatment. However, no LIP-tES pulses will be sent from the IASIS system during sham treatment, based a code entered to the system. A Staff Research Associate (SRA) #1 will assign a mTBI participant to either the mTBI-IASIS or the mTBI-Sham group, with an attached code from an existing IASIS code bank. Then, the IASIS treatment operator (SRA #2) who is blind to the group assignment will enter the code to the IASIS system during treatments. Based on the code, IASIS system automatically load the protocol for either IASIS or Sham treatment. Only at the end of the study (after Visit 16), the group assignment is revealed. Therefore, both the participant and IASIS treatment operator (SRA #2) are blind to the group assignment during the study.

D.4.3. IASIS's immediate effect of slow-wave potentiation -- pre- and post-session rs-MEG changes: To achieve this goal, we will perform three pairs of pre- and post-session rs-MEG exams at the beginning , midpoint, and the end of the IASIS treatment course: in Visit 3 for the 1st IASIS session (S1), Visit 9 for the 7th IASIS session (S7), and Visit 14 for the 12th IASIS session (S12). The post-treatment rs-MEG will be performed within 30 minutes immediately after the treatment session. Two-factor mixed-design repeated measures ANOVA with covariates, equivalent to linear mixed effect model, will be applied for statistical analysis. We will: 1) assess the within-subject significance of the immediate slow-wave potentiation due to IASIS session by comparing the voxel-wise Z-score and total abnormal MEG Z-scores between pre- and postsession exams; and 2) assess the between-group treatment effect by comparing IASIS with Sham. The total abnormal MEG Z-score is calculated by summing up the Z-score from all voxels that showed statistically significant slow-wave generation. The dependent variables at both time points are either voxel-wise Z-scores or total abnormal MEG Z-scores, and the predictors are time (pre- and post-session), group (IASIS versus Sham), and their interaction. Veterans receiving IASIS treatment but not sham are expected to show significantly increase rs-MEG slow-wave generation in post-session rs-MEG exam immediately after the treatment session (Hypothesis 2). The preliminary result in C.5 (Fig. 5) supports this hypothesis.

D.4.4. Ultimate slow-wave reduction following the IASIS treatment course -- pre- and post-treatment rs-MEG exams: Participants in mTBI-IASIS group will participate in the 6-week IASIS treatment, whereas those in mTBI-Sham group will participate in a sham treatment for the same time period. To assess the ultimate effect of the IASIS treatment course, the 1-week post-

treatment follow-up rs-MEG in Visit 15 will be compared with the baseline rs-MEG in Visit 2 (Fig. 10). The focus of our analyses are the pre- and post-IASIS change in the abnormal MEG slow-wave generation for both voxel-wise Z-score maps and the total abnormal MEG Z-scores. Two-factor mixed-design repeated measures ANOVA with covariates will be used to: 1) assess the withinsubject treatment effect by comparing the voxel-wise Z-score and total abnormal MEG Z-scores between pre- and post-treatment exams; and 2) to assess the between-group treatment effect by comparing IASIS with Sham. Participants receiving IASIS treatment, but not sham, are expected to show significantly reduction in abnormal rs-MEG slow-wave generation in post- over pre-IASIS exams (Hypothesis 3). Preliminary result in C.6.2 and C.6.3 (Figs. 6B and 7) supports this hypothesis.

D.4.5. Assessing Efficacy of Nexalin Treatment on a Subset of Veterans with mTBI and remaining PCS after IASIS Treatment: Participants in the mTBI-IASIS group who have participated in the 6-week IASIS treatment and who mention they have persistent PCS in a follow-up phone interview will be offered Nexalin Treatment. Nexalin TES or Sham TES will be administered once per day, Monday through Friday. Participants will receive 10-20 treatments, 3-4 times a week for 4 weeks, or up to 5 times a week for 4 weeks. All procedures were performed at Dr. Huang's office at VASDHS or at the UCSD RIL (prior to the move out of RIL) and were administered by Research Associates who will be specially trained on using the Nexalin equipment. Nexalin TES involves placing three conductive pads on the head (one on the forehead and one behind each ear). The patient then sits as the device administers the current through the pads. The waveform generated by the Nexalin device is a high frequency square wave (100 kHz), which has its amplitude modulated at a frequency of 4Hz, 40Hz, and 77.5 Hz. Amplitude of the waveform is controlled to range from **0 to 15 mA peak current**. Each treatment session will last for 60 minutes. The treatment is not expected to be painful, but some individuals may experience discomfort at the sites of the pad electrodes (i.e. tingling and burning). In most cases, patients cannot feel when the pads are activated. The Sham treatment will be identical with the exception that there will be no current through the electrodes. Since the Nexalin treatment is undetectable, this will exactly mimic active treatment. Pre-and post- MEG's will be administered. Also, the same questionnaires used during the IASIS treatments will be administered on a daily or weekly basis, depending on the questionnaire's instruction.

D.5 Study Changes in PCS and PTSD Severity due to IASIS (Aim 2)

We will study clinical symptom changes due to IASIS treatment. In both mTBI groups, RPQ and NSI will be used to assess PCS and their changes due to IASIS/Sham treatment. Since PCS will be assessed in all visits, we can trace the PCS change across the entire treatment course. Of course, the most important comparison will be the PCS between 1-week post-treatment follow-up (Visit 15) and the baseline (Visit 2) exams. Again, two-factor mixed-design repeated measures ANOVA with covariates will be used to: assess the within-subject significance of the PCS changes between pre- and post-treatment exams; and 2) to assess the between-group treatment effect by comparing IASIS with Sham. The dependent variables at both time points are PCS scores, and the predictors are time (pre- and post-treatment), group (IASIS versus Sham), and their interaction. We predict that compared with the sham group, mTBI Veterans received IASIS treatment will show significantly greater decreases in PCS symptoms between baseline and post-treatment assessments (Hypothesis 4). The preliminary result in C.6.1 (Fig. 6A) supports this hypothesis.

Besides RPQ and NSI, we will use the same statistical approach to examine IASIS-related changes in additional symptom measures: CAPS-5 and PCL-5 for PTSD symptoms, PSQI for sleep problems, and MGPQ for pain. Since brain injury increases the likelihood of both PCS and PTSD, we hypothesize that by treating the mTBI aspect using IASIS in Veterans, PCS will improve, and that PTSD symptoms will be reduced as well (Hypothesis 5, C.6.1), consistent with a model in which TBI impairs functioning of prefrontocortical and networked systems that are believed to be integral for inhibiting fear responses and promoting fear extinction [26,79]. False discovery rate (FDR) will be used to correct family-wise error [85].

D.6 Correlating IASIS Related Changes in MEG with Symptoms and Neuropsychological Exams (Aim 3)

Correlating IASIS-related changes in MEG slow-wave source imaging and PCS in mTBI: Correlation analyses will be performed to examine the neuronal correlates of changes in MEG slow-wave generation and PCS scores in Veterans with mTBI in both IASIS and Sham groups. Specifically, we will correlate the changes in the total abnormal MEG Z-scores as well as voxel-wise Z-score MEG source imaging measures with changes in PCS due to IASIS treatment, by comparing PCS scores from post-treatment follow-up (Visit 15) with the baseline (Visit 2) exams. We predict that reduction in MEG slow-wave generation will correlate with reduced total PCS score as well as specific symptom scores (e.g., sleep disturbance, post-traumatic headache, photophobia, and memory problem symptoms) (Hypothesis 6). The voxel-wise analysis may provide important spatial information of the slow-wave generation related to each PCS category. Linear regression analyses will be performed for the correlation analysis, and FDR will be used to control family-wise error [85] using correct $q < .05$. We predict that in mTBI-IASIS group, but on

in the sham group, reduction in MEG slow-wave generation will correlate with reduced symptoms. Preliminary data presented in Section C.6.2 and Fig. 6C support this hypothesis.
Correlating IASIS-related changes in MEG slow-wave source imaging and cognitive functions in mTBI: We will study the relationship between changes in MEG slow-wave generation with those in neuropsychological exam scores between post-IASIS (Visit 15) and baseline exams (Visit 2). For neuropsychological tests that differentiate HC and mTBI groups, we will perform linear regression analysis, where treatment-related changes
in neuropsychological test scores are used to predict the changes in MEG measures including voxel-wise slowwave Z-score (FDR corrected for family-wise error) and the total abnormal MEG Z-scores. We also predict that in mTBI-IASIS group, but on in the sham group, reduction in MEG slow-wave generation will correlate with improvement in the different cognitive domains that govern functioning.

D.7 Examining the effects of Covariate Variables on IASIS treatment and Exploratory Analyses in mTBI
Covariate variables to be included in above statistical analysis: Age, gender, education, combat exposure (DRRI-2), socioeconomics, OSU TBI-ID for lifetime history of TBI, ASSIST and AUDIT for alcohol and substance uses, and order of mTBI to PTSD will be added as covariates in the linear regression and ANOVA analyses in Sections D.4 - D.6. However, since these variables will be matched during our group assignment, we do not predict they will have major impact to the results of statistical analyses.
Exploratory studies: We will add 10 minutes rs-fMRI in Visit 2 to our existing MRI acquisition on a 3T system in the two mTBI groups, and use the data for exploratory FC analyses of the relationship between rsfMRI and rs-MEG using the approach described in [14]. We will also add an N-back MEG task in Visits 2 and 15 for exploratory analyses of changes in working memory function due to IASIS treatment. We have previously found that changes in rs-MEG neural patterns are highly associated with the working memory performance of the N-back MEG task [110].

D.8 Description and Justifications of Sampling Plan, Power Analysis, and Time Table
For assessing the specificity (1- false-positive rate) of the MEG slow-wave measures on a single-subject basis, the number of HC subjects in the normative database has to be sufficiently large. N=75 will allow us to reliably assess the normative datasets from HC participants. By choosing K=3 in the K-fold cross-validation approach, 2/3 (N=50) will be used to construct the normative database and the remaining 1/3 (N=25) to test
the specificity, with reliable performance.
Power analysis: We don't expect that one set of sample sizes will meet the needs of all 3 aims and 6 hypotheses equally well. Hence, for a proposed set of sample sizes, some hypotheses may be overpowered whereas the others may be adequately powered. We used G*Power (University of Dusseldorf) for the power analysis. The power analyses below show that the N=50 in each of the two mTBI groups (i.e, mTBI-IASIS and mTBI-Sham) provides a good balance for all the hypotheses. For Hypothesis 1, our voxel-wise MEG slowwave source imaging is expected to show substantially higher sensitivity in detecting in mTBI groups than conventional MRI. Based on our preliminary data using McNemar's test in C.2, we expect a large effective size (odds ratio > 50). At two-tailed, =0.01, N=50 in each of the mTBI groups, the estimated power is > 0.98. We also predict high test-retest reliability of MEG slow-wave source imaging measures in N=100 Veterans (50 in each group) that will have two consecutive MEG exams (Visits 2 and 3). Based on our preliminary data in C.4, high level of test-retest reliability (i.e., ICCs ≥ 0.75) is expected in our rs-MEG slow-wave source imaging. In Hypothesis 2, we predict that IASIS treatment will enhance neural healing by initially potentiating slow-wave generation immediately after each treatment session. In Hypothesis 3, we expect that in Veterans in mTBI-IASIS group, but not in mTBI-Sham group, MEG source imaging (voxel-wise and total Z-score) will ultimately show a significant decrease in abnormal slow-waves between pre- and post-treatment exams. Based on preliminary data in C.5 and C.6 (Figs. 6B and 7), for Hypotheses 2 and 3, we expect large effect size (Cohen's f>0.45). At two-tailed, =0.01, N=50 in each of the mTBI groups, the estimated power is > 0.98. In Hypotheses 4 and 5, we predict that, compared with the sham group, mTBI participants in the IASIS treatment group will show significantly larger decreases in PCS and PTSD symptoms between baseline and post-treatment assessments. Based on pilot data in C.6 and information from [68], we expect medium-to-large effective side for total the RPQ (Cohen's f>0.38) and medium-to-large effective size for PCL (Cohen's f>0.32). At two-tailed, =0.01, N=50 in each of the mTBI groups, the estimated power is > 0.95 for total RPQ score, and power > 0.85 for PCL. We will also have power > 0.88 for 5 individual PCS scores (e.g., PSQI for sleep problems, MGPQ for pain, etc.) with the conservative Bonferroni correction. For Hypothesis 6, we expect changes in MEG slowwaves will correlate with PCS scores and cognitive deficits in specific domains in mTBI groups due to IASIS. Based on our preliminary data in C.6 and C.7, we expect medium-to-large effect sizes (|r| ~ 0.4-0.8). With N=50 in each mTBI group, two-tailed, =0.05, the estimated powers are > 0.85 for changes in MEG slow-wave correlating with total PCS score or one NP variable. The same level of power can be achieved for 5 symptom individual PCS / NP variables at =0.05, in the conservative case of Bonferroni correction, and for more than 5

neuropsychological / symptom variables when using FDR correction. **Time Table of Tasks: See attachment.**

D.9 Combining data from pilot study, H150047

In order to complete data analysis with a larger sample size, we plan to combine data from pilot study H150047 for future analysis and publications. The data that will be combined will only be de-identified data from neuropsychological testing, IASIS treatments, MEG sessions, and MRI scans,using study numbers. Participants from this pilot study will not be re-consented and no waivers or consent or authorization will be needed in order to use the previously collected de-identified data.

Phase Orange COVID-19 Adaptions:

In compliance with VASDHS Policy, in-person interaction with research subjects during the COVID-19 pandemic, Phase Orange, will be limited to activities only viable if conducted in-person. Data collected in-person will be limited to consenting, MEG and MRI scan sessions, as well as IASIS, Nexalin, and/or TUNS treatments. Other aspects of participation, to include questionnaires, clinical interviews, and neuropsychological tests not requiring in-person interaction may be conducted remotely via phone. If appropriate or preferred by volunteers, forms, questionnaires, clinical interviews, and neuropsychological testing can be conducted in a private room, or outside (e.g., car, etc.) when performed in conjunction with an in-person study session, or in a testing room with appropriate social distancing, personal protective equipment (PPE), and sneeze guards. These adaptions will not change the data collected by this study (aside from the temporary removal of the TOMM, DEKFS Trail-making, WAIS-IV Symbol Search, WASI Matrix, DKEFS Color Word Interference, and WAIS-IV Digit Symbol Coding the neuropsychological testing battery due to concerns over shared surfaces and materials if neuropsychological testing was collected over the phone), and will allow the study to operate in full compliance of Phase Orange guidelines.

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 Classification Name: Device, Biofeedback
510(K) Number: K971708
Device Name: PHYSIOLOGICAL MONITORING & BIOFEEDBACK TRAINING DEVICE
Applicant: J & J ENGINEERING, INC.
55 Northern Blvd., Suite 410
Great Neck, NY 11021
Contact: Anand Akerkar
Regulation Number: 882.5050
Classification Product Code: HCC
Date Received: 05/08/1997
Decision Date: 02/18/1998
Decision: Substantially Equivalent (SE)

Device Classification Name: Stimulator, Cranial Electrotherapy (21 CFR 822. 5800)
Trade/Device Name: Transcranial Electrotherapy Stimulator-A. Model TESA-1
510(K) Number: K024377
Applicant: Kalaco Scientific, Inc.
6514 N. 85th Place
Scottsdale, AZ 85250-5742
Contact: Raymond R. Wallage
Regulation Number: 822.5800
Classification Product Code: JXK
Date Received: 12/25/2002
Decision Date: 04/22/2003

Status:
These biofeedback device and TES device will be stored at VASDHS.

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.***

California Verbal Learning Test, (CVLT)
Delis DC, Kramer JH, Kaplan E, and Ober BA, California Verbal Learning Test–Second Edition. The Psychological Corporation, San Antonio, TX, 2000

Weschler Adult Intelligence Scale: Symbol Search, Coding, Digit Span, (WAIS-IV)
Wechsler D, WAIS-IV Wechsler Adult Intelligence Scale. The Psychological Corporation, San Antonio, TX, 2008.

Weschler Abbreviated Scale of Intelligence (WASI): Vocabulary, Matrix Reasoning. The Psychological Corporation by Harcourt Assessment, Inc., TX, 1999,

Delis-Kaplan Executive Function System: Verbal Fluency, Trail-Making and Color-Word Interference, (DKEFS)
Delis DC, Kaplan E, and Kramer JH, Delis-Kaplan Executive Function System. The Psychological Corporation, San Antonio, TX, 2001.

Connors Continuous Performance Task II, (CPT-II)
Conners CK, Conners' Continuous Performance Test–II. Multi-Health Systems, North Tonawanda, NY, 2000.

Wechsler Test of Adult Reading, (WTAR)
Holdnack TA, Wechsler Test of Adult Reading. Psychological Corporation, San Antonio, TX, 2001.

Test of Memory Malingering, (TOMM)
Tombaugh TN, Test of Memory Malingering. Multi-Health Systems Inc., North Tonawanda, N.Y., 1996.

Neurobehavioral Symptom Inventory, (NSI)
King PR, Donnelly KT, Donnelly JP, Dunnam M, Warner G, Kittleson CJ, Bradshaw CB, Alt M, and Meier ST. Psychometric study of the Neurobehavioral Symptom Inventory. J.Rehabil.Res.Dev. 49: 879-888, 2012.

Clinician Administered PTSD Scale, (CAPS)
Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, and Keane TM. The development of a Clinician-Administered PTSD Scale. J.Trauma Stress. 8: 75-90, 1995.

Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ)

PTSD Checklist - Civilian Version (PCL-C)

Multidimensional Fatigue Symptom Inventory - Short Form (MFSI-SF)

Beck Depression Inventory (BDI-II)

Beck Anxiety Inventory (BAI)

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.

At our research site, we will implement a system for appropriate oversight and monitoring to ensure safety and welfare of the participants and validity of the data in the form of a Data and Safety Monitoring Board (DSMB). This DSMB will provide oversight and review of our project. Its responsibilities will include: reviewing protocols, informed consent/assent documents and plans for data safety and monitoring; evaluating the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the project, and other factors that can affect study outcome; considering factors external to the study such as scientific developments that may have an impact on the safety of the participants or the ethics of the project; protecting the safety of the study participants; reporting on the safety and scientific progress of the project;

making recommendations to the PI, IRB and the VASDHS concerning continuation, termination or other modifications of the project based on any
adverse events of the study; and ensuring the confidentiality of the data and the results of monitoring. The DSMB will consist of four individuals, who are not affiliated with the research team, who do not have scientific, financial or other conflicts of interest with the project, including researchers in MEG and MRI, and a biostatistician/ methodologist. The DSMB will meet via teleconferences twice per year, with additional meetings convened at the discretion of the VASDHS-IRB Chair or any of the DSMB members, if deemed necessary.

The DSMB will meet every 6 months to discuss any AE/SAE events and any discoveries of significant new information during data analysis. DSMB reports will be provided to the IRB every 6 months.

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***

The MEG will be acquired at UCSD's Qualcomm Institute (QI) inside Atkinson Hall under a fee-for-service contract. QI is the UC San Diego division of the California Institute for Telecommunications and Information Technology (Calit2), one of four Gray Davis Institutes for Science and Innovation located on University of California campuses. QI brings together more than 150 faculty members, nearly 120 technical and professional staff on the UC San Diego campus, as well as hundreds of student workers, undergraduate scholars, graduate fellows, postdoctoral researchers, project and research scientists, and nearly 200 industry partners to date. The institute's strategic vision stresses collaborative, interdisciplinary research in four core areas to benefit society: culture, energy, the environment, and health. QI also prototypes and builds enabling technologies (wireless, photonics, cyberinfrastructure, and nano-micro-electromechanical systems, or nano-MEMS). In addition, the institute plays a leadership role in the development of new institutes and research centers for the UC San Diego campus, on topics ranging from robotics and the brain to design. QI is a 6 minute drive from the VASDHS.

During the MEG session, subjects will perform tasks. These include: sitting still with their eyes open and then closed for three 5 minute sessions, making decisions using hand movements while completing performance tasks and looking at words or letters on a screen. All tasks are non-invasive (pain-free).

The MRI scans will be acquired at UCSD Center for Functional MRI (CFMRI) under a fee-for-service contract using their state-of-the-art research dedicated GE Discovery MR750 3T Scanners. These scanners provide specific pulse-sequences that this research group has used for the last 4 years. CFMRI is an imaging resource and recharge CORE facility for the San Diego scientific community dedicated solely to research. The CFMRI occupies an approximately 7,000 sq. ft. (assignable) building on the main UCSD campus adjacent to the Basic Science Building and the animal vivarium, and is a 5 minute walk from the VASDHS. Aside from the two GE 3T scanners, the CFMRI also currently houses:, one 7T Bruker small animal MRI scanner, and a mock MRI scanner. These systems support approximately 40 ongoing research projects for the San Diego research community, including investigators from the VASDHS, UCSD, the Salk Institute, the Scripps Research Institute, and San Diego State University.

The VASDHS houses a 3T clinical MRI scanner. The VASDHS MRI scanner can only be operated by a certified VA MRI technician, but the facility has not hired a VA MRI technician for performing research MRI scans. If arrangements allow the study perform scans at the VASDHS, the study will transfer MRI scans from CFMRI to VASDHS rather than requesting sole source procurement for a service contract from UCSD's Department of Radiology.

We have received the approval from the VA Rehab R&D for a partial off-site space waiver that allows us to use offsite locations for: a) pre-processing the MEG and MRI data for removing artifacts and head movements.

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.**

Inclusion Criteria:
175 subjects in three groups: Two groups contain OEF/OIF/OND Veterans (age 18-60) diagnosed with chronic mTBI with persistent PCS (majority due to blast). Veterans in these two groups will be matched on age, gender, education, combat exposure, symptom chronicity, and socioeconomics. Group 1 (mTBI-IASIS group, N=50) contains mTBI Veterans to be blindly assigned to a 6-weeks IASIS treatment with two sessions per week. Group 2 (mTBI sham group, N=50) contains mTBI Veterans to be blindly assigned to a sham treatment for 6 weeks with also two sessions per week. Veterans with mTBI in both Groups 1 and 2 must currently have persistent PCS at least 6 months post injury (i.e., the most recent injury). In addition, PTSD symptoms will be assessed and matched in symptom severity and diagnostic category in the two mTBI groups. Group 3 (control group, N=75): age-, gender-, education-, combat exposure-, and socioeconomically-matched HC Veterans. After completing 6 weeks of IASIS treatment, any Veteran participants in Group 1 who still mention or complain of remaining PCS in their month follow-up phone interview will be offered Nexalin treatment at no cost to the participant.

Exclusion Criteria:
1) history of other neurological, developmental, or psychiatric disorders (based on the DSM-5 (MINI-7) [86] structured interview), e.g., brain tumor, stroke, epilepsy, Alzheimer's disease, schizophrenia, bipolar disorder, ADHD, or other chronic neurovascular diseases such as hypertension and diabetes; 2) substance or alcohol use disorders according to DSM-5 [87] criteria within the six months prior to the study; 3) history of metabolic or other diseases known to affect the central nervous system (see [88] for similar criteria); 4) Metal objects (e.g., shrapnel or metal fragments) that fail MRI screening, or extensive metal dental hardware (e.g., braces and large metal dentures; fillings are acceptable) or other metal objects in the head, neck, or face areas that cause non-removable artifacts in the MEG data; 5) Potential subjects will be administered the Beck Depression Inventory (BDI-II) to evaluate level of depressive symptoms, and suicidal ideation; any participant who reports a "2" or "3" on the BDI–II: item 9 (suicidal thoughts or wishes) will also be excluded. However, depression following mTBI or traumatic event of PTSD is common [89]; therefore, in two mTBI groups, we will include and match patients with depression symptoms reported after their injury/event, and will co-vary BDI-II score in data analyses.

Section 10.6 Avoiding coercion of students or employees

10.6) Indicate how coercion of students and/or employees will be avoided:

The fact that someone may be a student or employee is not relevant to participation in the study. These individuals are not targeted for inclusion and their student or employee status will not be recorded in the study. All students or employees must be Veterans to participate.

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.

Recruitment will be done by Co-Investigator, Dr. Scott Matthews, who is the head psychiatrist at the Aspire Center, a veteran residential rehabilitation program, who sees several veterans with TBI and/or PTSD. Further recruitment will also be done by referrals from other Co-Investigators, such as Dr. Dewleen Baker, psychiatrist at the main VA hospital, and by VA IRB approved Recruitment Flyers. If someone shows interest in being in the study, then they will contact Dr. Huang (PI), Dr. Matthews or (Co-I), or other co-investigators and more information will be provided.

Furthermore, 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.

Another of our original methods is to post VA IRB approved flyers/brochures around the local community and within Veteran support group locations. Due to the Covid pandemic, many of these community groups have been meeting online (via Zoom or other video-chatting resources), rather than in person. In order to amplify our research, we plan to ask Veteran support groups and other community groups to post our VA IRB approved flyers/brochures on their own websites and social media. PLEASE NOTE that these groups will not collect any personal information from potential participants on our behalf. Furthermore, no personal social media accounts nor lab accounts will be used for recruitment.

A potential participant will undergo phone screening to determine eligibility. If they are eligible to participate at determined by the phone screening, they will come to the site to be consented. There they will sign the Consent Form, HIPAA Form, and a Release of Information (only if needed) before the brain imaging, Neuropsychological testing, and MHA sessions begin.

The specific personal information that will be voluntarily released by the potential participant, through phone screening, includes: information on any traumatic brain injury or concussion or PTSD history and information regarding inclusion and exclusion criteria.

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.***

We will have VA IRB approved and stamped Recruitment flyers, brochures, and a VASDHS TV advertisement available. We are no longer enrolling for this study, and therefore not advertising it.

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.

Interested participants will contact the study coordinators for screening. Screeners will describe the study, stress the importance of participation being voluntary, and ask study questions, inclusion and exclusion criteria, in order to place the subject in a specified group. If the interested participant passes all inclusion criteria, he or she will be asked whether they want to participate. The study coordinator will work with the subject to schedule the MEG, MRI, neuropsychological testing, and mental health assessment.

During their first visit at VASDHS the PI or study coordinators will explain the study, answer any questions, and have the participant sign a consent form.

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.

Waiver of informed consent is requested in order to obtain information for screening and recruiting purposes. Interested Veterans will contact the study coordinator in order to complete phone screening. During the phone screening process, the coordinator will explain the study and criteria and ask the interested Veteran specific criteria questions pertaining to history of their TBI and/or PTSD event(s), if any, and their age, and any history of claustrophobia, metal in their head, neck, or spine, neurological conditions, alcohol abuse, drug abuse, and ADD/ADHD as this information may affect their eligibility to participate in this study.

Section 12.6 Decisional Capacity Assessment

12.6a) Describe the method(s) for determination of decisional capacity: (see ? for guidance) ***Please note that documentation of the assessement is required.***

In case we detect any sign that an mTBI participant or healthy control participant may have difficulty consenting, a decisional capacity assessment has been devised for all subjects. It is a brief, post-consent paper-and-pencil test covering the purpose of the study, MEG and MRI safety, privacy and de-identification of data. For those prospective subjects who respond incorrectly to one or more of the questionnaire items, the missed items will be discussed and the questionnaire re-administered. For prospective subjects who have reservations or who demonstrate impaired decisional capacity by an incorrect response to one or more items on two separate attempts, the enrollment process will be terminated.

12.6b) If subjects with limited decisional capacity will be enrolled, describe methods for obtaining subject assent or why they are not indicated:

Subjects with limited decisional capacity will not be enrolled.

12.6c) If subjects with limited decisional capacity will be enrolled, describe procedures for respecting subject dissent and any additional safeguards or why these features are not needed:

Subjects with limited decisional capacity will not be enrolled.

12.6d) If subjects with limited decisional capacity will be enrolled, describe the risk and, if greater than minimal, the relation to potential benefits:

Subjects with limited decisional capacity will not be enrolled.

12.6e) If subjects with limited decisional capacity will be enrolled, describe the justification for the inclusion of any incompetent persons or persons with impaired decision-making capacity:

Subjects with limited decisional capacity will not be enrolled.

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.

Phone screening, prior to enrollment in the study is required to determine whether the interested participant fits the study's inclusion/exclusion criteria. Phone screening will include the following identifiers and health information: participant's name, phone number, and any criteria pertaining to TBI and/or PTSD. We need a HIPAA waiver to be able to complete the phone screening.

The entire Phone Screening is brief, concise, and minimal risk. Specifically, this screening contains the 1) Phone Script naming Dr. Mingxiong Huang or the study coordinators as the screeners and giving a simple explanation of IASIS Micro Current Neurofeedback, 2) A listing of subject criteria to read to the interested participant, 3) Three questions for inclusion criteria pertaining to TBI and PTSD, 4) Five exclusion criteria questions, 5) Contact Information requesting phone number.

Also, 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 we can contact the Veteran via his or her preferred method of contact for phone screening.

Participants will sign the HIPAA form after being enrolled and signing the consent.

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 code that identifies the participant's name with the research study number will be kept in a locked cabinet, separate from the participant data and separate from the non-identifiable participant data, in Dr. Huang's office at VMRF, 13-407. This code will also be placed on Dr. Huang's R:/drive on the secure VA network and will be accessible only to the study staff.

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:

Data will only be destroyed according to RCS-10 under Records Control Manager guidance.

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 HIPAA waiver is requested because during phone screening, inclusion and exclusion questions will be asked to determine whether interested subjects will be able to consent/enroll in the study. These questions include any TBI or concussion, PTSD diagnosis, claustrophobia, unremovable metal in body/head, neurological conditions or conditions that can affect the brain, diagnosis of ADD/ADHD, and pregnancy.

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)

The HIPAA waiver is required to complete the phone screening, so that inclusion and exclusion criteria (listed in 12.10f) can be used to determine whether the interested participant can be enrolled/consented.

Section 13 - Alternatives to Participation

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

There are no comparable alternative treatments of that we know. No other neurofeedback methods or treatments will be used. This treatment is not available to veterans with mTBI without participating in this study. The only alternative is not to participate in this study. This study is completely voluntary.

Section 14 - Potential Risks

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

Potential Risks from MEG and MRI: MEG is a completely non-invasive functional imaging technique. There are no known dangers from MEG measurements. There are no known dangers from MRI either, given standard thorough screening for metal, cardiac pacemaker, etc. However, subjects with extensive dental work
tend to generate strong metal artifacts that may saturate MEG sensors or overshadow the neuronal MEG signals even after being degaussed. Thus, a "noise-run" of 2-3 minutes will be performed before the actual MEG recording on every subject to ensure the quality of the data. If the noise-run shows strong metal artifacts, the subject will be degaussed and a second noise-run will be performed. The deguassing process entails holding a hand-held device (degausser) near the participant's mouth and moving the device in a swaying motion away and towards the mouth for 1-2 minutes. This essentially removes the magnetic properties of any metallic dental work (crowns, fillings, posts, etc.) that lasts for a few hours. This is a non-invasive procedure allows the MEG to collect better quality/cleaner data. The device never touches the participant.
If strong artifacts persist in the second noise-run, the subject will be excluded from the study. On the other hand, subjects with metal objects in their body (below their shoulders) or with non-extensive dental work (e.g., fillings) should not be excluded since MaxFilter and ICA can remove these artifacts. However, subjects who do not meet safety requirements for MRI
(e.g., patients with cardiac pacemakers) will be excluded. As the MRI effect upon early development of the fetus is not completely known, pregnant females will be excluded as well.
There are some minor risks to the subjects who pass the screening process as listed below:
1) Fatigue or discomfort: during the MEG procedure, subjects may experience discomfort from sitting motionless during the recording process. Subjects may become fatigued during neuropsychological testing and breaks will be provided as needed.
2) Noise during MRI exam: the magnet makes a loud, banging noise when collecting images. This is likely to be encountered by all subjects.
3) Claustrophobia: subjects may feel anxious in the confined space of the MRI magnet's bore. Although we screen carefully for this, there may be a slight possibility that a subject who is not normally anxious in small places might become anxious in the magnet.
4) Risk of violation of the right to privacy: subjects' data or diagnostic status could become known by others outside the research team. This is highly unlikely but the possibility is not zero.

Potential Risks from EEG Measurements during IASIS: EEG is a minimal risk procedure. There

are no published risks involved in EEG recording or EEG-biofeedback. Some rubbing alcohol and minimally abrasive preparation gel may be used on skin areas of the face or head for electrode placements. If abrasion is
accidentally too strong, there is a slight risk of infection, but because of the high impedance electrodes used here, much less abrasion will be necessary to obtain a clean signal than was necessary with older EEG systems. All instruments will be sterilized between each subject and study staff will thoroughly wash their hands between subjects to diminish any chance of infection. However, because of the 30-min duration of the testing session, subjects may experience some level of unease or discomfort due to the inability to walk around during the session. To avoid such discomfort, we will advise all subjects that if they should feel the need to get up and walk around during the session that they should alert the experimenter immediately and they will be
unhooked from the EEG amplifier.

Potential Risks from IASIS Current Neurofeedback Intervention: Temporary side effects are primarily feeling tired, wired (slightly anxious), spacey, lightheaded, or a mild headache. Nausea can also be a temporary side effect. It is possible that some of the participant's current symptoms may very briefly flare up. These side effects are mild and temporary, and last a few minutes to a few hours, occasionally a day and rarely a few days. If participants exhibit any side-effects, they will be monitored for about 15 minutes after the session before being sent home. IASIS treatment does not pose a risk or hazard for operating a motor vehicle.
There are no alternative treatments comparable to IASIS that we can provide. The only alternative is not to participate in this study.

Potential Risks from Nexalin: Transcranial electric stimulation devices are classified as a Class III device. These types of devices have been used for many years and occasional adverse effects have been reported, including: headache, nausea, minor burns, increased agitation, minor rash from specific electrodes, and electrical discharge when electrodes are removed. Specifically, headaches and nausea have been noted when current levels are higher than those used in the present study. Note: the device settings for current and duration of treatment are fixed (i.e., cannot be altered by the administering clinician or technician). Since the Veteran participant will already have had IASIS, there are no other alternative treatments comparable to Nexalin that we can provide. The only alternative is not to participate.

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.

The following procedures will be used to minimize the risks explained above.
1) For every participant that is enrolled, he/she will undergo screening to qualify for the study that includes a detailed review of possible metal in his/her body (see screening form in appendix). Every participant will also be examined by a hand-held metal detector before entering the MRI scanner. If
the participant has any metal in his/her body that interferes with the safety of the subject, he /she will not be enrolled in the study.
2) Subjects' head and neck will be padded and legs supported to make him/her as comfortable as possible during both MEG and MRI exams. Two-way intercom is available for both MEG and MRI. Unlike the MRI, there is no window on the MEG shielded room, so a video camera will be used inside the shielded room to monitor the subjects. No recordings of images during video camera monitoring while in the MEG shielded room will be performed or retained. For the MRI scans, the subjects will be provided with sound-attenuating ear-plugs before the imaging session and instructed on their use.
3) Subjects will be screened for claustrophobia. Those with claustrophobia will be excluded. Subjects may communicate with the operator of the scanner through the intercom at any time. The subject may request at any time that the experiment be terminated.
4) Members of the research team will be available to discuss any upsetting or discomforting emotions. If there appears to be a high level of upsetting or discomforting emotions during the study, or a high level of symptoms, as determined during CAPS interview, then a detailed assessment by the study
licensed clinician as well as the study investigator (Dr. Baker) may occur, where various options (such as referral to the subjects clinician or the VASDHS same day clinic) will be provided.

Additionally, should a participant report a "2" or "3" on the Beck Depression Inventory–II: item 9, regarding suicidal ideation, study procedures will include a brief assessment for safety by the study licensed clinician (psychologist) with consultation with Dr. Baker. Unless there is clear and imminent risk to the life of the Veteran, full confidentiality will be maintained. If subject safety is a concern, the subject will be referred to further treatment, and will be removed from the study.
5) To protect the privacy of study participants, an identifier card with a unique subject number will be created for each subject. All identifiable data will be recorded only on this card and the card will be destroyed upon completion of data analysis for the study. Subjects will be identified only by the unique subject number on all other data collection forms and in study databases. Throughout the term of the study, identifier cards will be kept in a locked file cabinet in a separate room from the study data. MRI data files are also identified by the date of the scan. Multiple subjects run on the same date are denoted with a letter suffix, e.g., 04_05_10a, 04_05_10b. MEG and MRI data are stored on network devices that are protected by passwords and firewalls. The likelihood of a study participant's identity being associated with any of the subject's data is extremely remote.
6) In case of any adverse medical event as the result of participating in this research, VASDHS will provide necessary emergency care.
7) Psychological Discomfort: Our interviewers are trained to allow subjects not to answer questions that seem to be distressing them and to terminate as indicated on clinical grounds, to allow participants to refuse to answer questions that make them uncomfortable, or to withdraw from the study.
8) Results of tests (i.e., mental and physical assessments) and scans (MRI and MEG) will remain confidential under all circumstances. Exception to confidentiality is for participant benefit and serves the purpose of facilitation of treatment in the event there is (1) a clear and imminent risk of
danger to self (suicidal ideation with plan) (2)MRI scans will receive a routine examination by a study investigator (Dr. Roland Lee). The MRI procedures used in this study are for research and no clinical report will be generated from this study. In the event of incidental findings/lesions with clinical significance in MRI scans (e.g., tumor, stroke, etc.), the PI, Dr. Mingxiong Huang, or Co-I, neuroradiologist Dr. Roland Lee, will notify the participant and the participant's medical provider via phone call. These findings may cause the participant additional tests. The decision whether to proceed with further examinations will lie with the participant as there are no opportunities for clinical follow-up studies as part of this research. Additionally, phone contact with the subject, subject's medical provider, and the subject's response will be documented as a CPRS note. Otherwise, all results of non-incidental findings will be kept confidential.
9) Members of the investigative team will be thoroughly trained regarding the protection of patients' rights to confidentiality. Identities of participants will not be revealed in the publication or presentation of any results from this project. Procedures specified in the consent forms are consistent with HIPAA regulations. All investigators and research staff will complete the VA human subject certification requirements, as well as certification in HIPAA regulations.
Safety of participants is ensured by procedures described in detail above. These procedures are supervised by a team of physicians, psychologists, physicists, and biologists with extensive experience in physical and mental health treatment, imaging, and psychophysiological testing. Briefly, participants are evaluated for co-morbid major psychiatric or substance use disorders and referred for care as indicated at baseline if they are not already members of a VASDHS clinic; those who enroll are assessed for deterioration of their clinical condition, distress, and suicidality, by the study psychologist and study physician, a psychiatrist
during study participation and those with psychiatric disorder or depressed mood or suicidality not already under a clinician's care will be referred as indicated.
With our previous and ongoing studies we have developed a standardized procedure for reporting findings of clinical significance. The appropriate clinician will be contacted in a referral process for additional imaging and clinical care. We work in close contact with the clinicians in the TBI clinic at the VA San Diego as well as multiple other VA network clinicians. Additionally, Co-Is Drs. Lee, Baker, and Matthews on the study are directly involved in clinical care and can make any necessary proper referrals.
10) To avoid headaches and nausea in Veterans using Nexalin, lower currents will be used. Participants shall also be instructed to alert the Research Associate if they experience headache or nausea. If the condition continues, treatment will be discontinued. Burn occurrence can be avoided by using lower current (as is in the case for this study), large area electrodes, and by the device's ability to monitor electrode impedance and stop treatment if electrode contact is poor. The device generates no DC current and thus no significant electrolysis will occur in the electrodes. The pulse-based AC waveform is passed through a charge blocking capacitor to participant electrodes for further participant protection. Rarely, participants have been noted to experience excitability or heightened nervousness during treatment. The Research Associate administering treatment shall be trained to identify such cases and instructed to decrease current or discontinue treatment as appropriate. If agitation persists for a participant, the Research Associate may discontinue treatment. Rashes from specific electrodes may occur in participants sensitive to the adhesives used. The possibility of such rashes or skin irritation has been minimized by maintaining charge balance in the output waveform so significant electrolysis does not occur at the electrode/skin interface, and by using glycerol coated electrodes that result

in little or no skin irritation. Additionally, collection of participant sensitivity information prior to treatment may avoid adverse reactions in patients with a prior history. Before
treatment, participants shall be instructed to alert the Research Associate if they experience any pain or discomfort. The Research Associate shall also examine the area of electrode contact before and after treatment and note any adverse reactions. Participants will be instructed not to remove electrodes during treatment. Electrodes and wires to the device shall be placed such that accidental removal of electrodes during treatment is unlikely. Finally, participants will be shown the "current off" button on the device and instructed to use this button if they feel it is necessary to terminate treatment prematurely.

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)

There are no direct benefits to the subject for participating in the brain imaging portion of the research. Broader scientific benefit, as discussed elsewhere in this application, is potentially large. Other benefit to
participants will be limited to their education as a result of self-report assessment and neuropsychological recording.
For the IASIS treatment portion of the research, the Veterans may experience reduced post-concussive symptoms (e.g., post-traumatic headache, photophobia, memory problems, and sleep disturbance symptoms), and improved cognitive functions. The procedures of the study involve minimum risk, as discussed above, and the risks encountered can be easily managed. Thus, the risk/benefit ratio favors the benefit.
For Veterans who complete the IASIS treatment, participants may experience reduced post-concussive symptoms, as listed in the paragraph above.

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.

The procedures of the study involve minimum risk, as discussed in Section 17: Potential Benefits, and the risks encountered can be easily managed. Thus, the risk/benefit ratio favors the benefit.

Section 20 - Compensation for Participation

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

As of 09/30/2022, funding for this study ended and participant study visits/sessions stopped.

During the data collection period, each participant received between $225 - $900 total for participation in MEG's ($75 each), MRI ($75 each), neuropsychological exam and mental health assessment ($75 each session), and IASIS or Sham sessions ($300).

If the Veteran participated in Nexalin treatments, he or she will received up to $500 for total participation. Specifically, they received $75 for every full hour of MEG and $25 per Nexalin session (amounting to $250-$500 for 10 up to 20 Nexalin sessions).

Controls underwent 1 NP/MHA visit, 1 MEG, and 1 MRI. A subset of controls will received a second MEG for retest comparison.

All particpants were compensated $40 per round trip visit to the UCSD RIL/UCSD CfMRI to cover transportation costs of gas, bus fare, ride sharing expenses, etc.

Particpants in the TBI group with IASIS neurofeedback received 1 NP/MHA visit, 1 MEG, and 1 MRI all at baseline/pre-IASIS, 12 IASIS sessions, 3 MEG's throughout the IASIS sessions, 1 post-IASIS MEG, and 1 post-IASIS NP/MHA. A subset of the TBI group with IASIS neurofeedback received 1 additional follow-up MEG one month post-IASIS.

Participants in the TBI group with SHAM IASIS completed 1 NP/MHA visit, 1 MEG, and 1 MRI all at baseline,/pre-Sham IASIS, 12 Sham IASIS sessions, 3 MEG's spread throughout the Sham

IASIS sessions, 1 post-Sham IASIS MEG, and 1 post-Sham IASIS NP/MHA.

Particpants in the TBI group with Nexalin TES received 1 MEG at baseline/pre-Nexalin, 10-20 Nexalin sessions, and 1 post-Nexalin MEG.

Participants in the TBI group with Nexalin-sham completed 1 MEG at baseline/pre-Nexalin, 10-20 Nexalin sessions (sham sessions will be administered), and 1 post-Nexalin MEG.

If a participant discovered that they were in an IASIS Sham, or Nexalin Sham condition, they may may have chosen to undergo the true treatment. If they did so, they were compensated in accordance with the respective values listed above for their treatment.

Subjects were offered a picture of their brain MRI containing 1 sagittal slice, 1 axial slice, and 1 coronal slice of their T-1 scan. Subjects were reminded that this picture is not completed for clinical purposes. Also, this picture would not contain any subject information nor any personal information.

Section 21 - Responsibilities and Qualifications

Here are the identified study staff members

Mingxiong Huang, PhD

Carl T. Rimmele, PhD, Deborah L. Harrington, PhD, Dewleen G. Baker, MD, Lu D. Le, DO, Roland R. Lee, MD, Scott Christian Matthews, MD, Sharon L. Nichols, PhD, Annemarie Angeles Quinto, Hayden B. Hansen, Jaqueline Hernandez-Lucas, Jared Baumgartner, Melita Maria D'Almeida, Qian Shen, PhD

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.

Dr. Mingxiong Huang*, Ph.D., (PI) has privileges at the VA and UCSD Medical Centers and will be in charge of the MEG and MRI.

Dr. Dewleen Baker*, M.D.,(Co-I) is a psychiatrist at the VA. She will assist in referring participants to this study.

Dr. Roland R. Lee, M.D., (Co-I) has privileges at the VA and UCSD Medical Center, and will be analyzing the MRI scans.

Dr. Sharon Nichols (Co-I) is a licensed neuropsychologist for UCSD. She will oversee the neuropsychological testing session for this pilot study.

Dr. Scott Matthews* (Co-I) is a psychiatrist for VA and UCSD. He will assist in referring participants to this study.

Dr. Lu Le* (Co-I) will be a source of subject recruitment, will review data and summary reports, will work on publications.

Dr. Deborah Harrington (Co-I) is a Research Scientist at the VASDHS. She will review data, summary reports, and work on publications.

Annemarie Angeles Quinto*, BA, is a VA San Diego research assistant/psychology technician and a UCSD Medical Center staff volunteer. She will assist with the MEG, MRI, neuropsychological data collection, and IASIS Micro Current Neurofeedback treatment.

Hayden Hansen*, BS, is a VA San Diego research assistant/psychology technician. He will assist with the MEG, MRI, neuropsychological data collection, and IASIS Micro Current Neurofeedback treatment.

Jared Baumgartner*, BS, is a VA San Diego research assistant/psychology technician. He will assist with the MEG, MRI, neuropsychological data collection, and IASIS Micro Current Neurofeedback treatment.

Jaqueline Hernandez*, BA, is a VA San Diego research assistant/psychology technician. She will assist with the MEG, MRI, neuropsychological data collection, and IASIS Micro Current

Neurofeedback treatment.

Melita D'Almeida, BS, is a VA WOC. She will assist with mental health assessments, data analysis, and publications.

*Staff members responsible for consenting subjects.

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.)

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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.

VA Merit I01 funds this study.

Non-VASDHS Research Collaborator:
Barry Bruder - provides the IASIS Micro Current Neurofeedback system. Mr. Bruder will not have access to subjects or any data.

Dr. David Dubin - will act as a consultant on the IASIS Micro Current Neurofeedback system. Dr. Dubin will not have access to subjects or any data.

Dr. David Owens - provides training on operating the system. Dr. Owens will not have access to subjects or any data.

Dr. Mark White - provides the Nexalin system as well as training on operating the system. Dr. White will not have access to subjects or any data.

Non-VASDHS Research Consultant:

Ashley Swan, Consultant - will work on data analysis and publications, will not have access to identifiable data/PHI

Ericka Foote, Consultant - will work on data analysis and publications, will not have access to identifiable data/PHI

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.

To protect the privacy of study participants, an identifier card with a unique subject number will be created for each subject. All identifiable data will be recorded only on this card and the card will be destroyed upon completion of data analysis for the study, according to RCS-10 under Records Control Manager guidance. Subjects will be identified only by the unique subject number on all other data collection forms and in study databases. Throughout the term of the study, identifier cards will be kept in a locked file cabinet in Dr. Huang's office in the VMRF building, 13-407. The information on these identifier cards will also be uploaded to Dr. Huang's R:/drive on the secure VPN.

The study collects data in the forms of consent, HIPAA, and demographic paperwork, coded neuropsychological paperwork, coded MEG data data in .fif files, and coded MRI data in CD's.

The consent, HIPAA, and demographic paperwork are kept in a locked cabinet in Dr. Huang's office, 13-407. The coded neuropsychological paperwork and coded MRI CD's are kept in a separate locked cabinet, in that same office. The coded MEG data, in .fif files, are stored on a Linux workstation, EE112983, located in 13-406. This workstation is the computer on the right-side of the office.

MRI data files are also identified by the date of the scan. Multiple subjects run on the same date

are denoted with a letter suffix, e.g., 04_05_10a, 04_05_10b. MEG and MRI data are stored on network devices that are protected by passwords and firewalls. The likelihood of a study participant's identity being associated with any of the subject's data is extremely remote.

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:

- [x] Protected Health Information (PHI)
- [x] Names
- [ ] Device identifiers and serial numbers
- [x] 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)
- [x] Telephone numbers
- [x] 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
- [x] 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

SSN numbers are required for Veteran participant payment: 1. To be placed on VA Form 10091 (VA-FSC Vendor File Request Form) and 2. in lieu of VA Form 10-7078 (R) (Authorization and Invoice for Medical and Hospital Services).
SSN numbers are also required to access and input CPRS records.

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 will be saved on a DVD labelled with the participant's research ID. All hardcopy DVD's will be stored in a locked cabinet at Dr. Mingxiong Huang's office, 13-407, located in the VMRF building on VASDHS grounds.

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

27.2b) 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 study laptop will used to generate computerized neuropsychological test data reports on password protected programs, to complete neurofeedback sessions, as well as to acquire data during scanning. This laptop (Dell Latitude D520) has been used since 2007 and therefore, has no VA EIL sticker. The current laptop does not connect to the internet but we will try to follow VA policy. We will work with Jim Christian in order to register this laptop into the VA EIL.

Another study laptop was purchased in 2019 under EIL 814, 664 EE113434, and will also be used to generate computerized neuropsychological testing data reports on password protected programs, to complete neurofeedback sessions, and to acquire data during scanning.

During the time of the study, both laptops were transported to the UCSD RIL and/or UCSD CfMRI for data acquisition during scanning and/or Neurofeedback treatment sessions but are now stored in a locked cabinet in Dr. Huang's VMRF office, 13-407. The laptop is used for data analysis, completed in the VMRF building.

A copy of the data on the VA laptop will be stored on Dr. Huang's VA Research Drive.

The coded MEG data, in .fif files, are stored on a VA Linux workstation, EE112983, located in 13-406. This workstation is the computer on the right-side of the office.

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).

For electronic but coded data stored in a computer: Study records entered into a computer system will be assigned code numbers and will not be individually identifiable (per VA handbook 1605.1 Appendix B). The key that relates the code numbers to the individuals will be kept in a locked cabinet in the research team's office in 13-407 at the VMRF building and destroyed according to an approved VA records control schedule. The key will also be stored on Dr. Huang's R:/drive and only accessible to study staff with VPN and PIV access.

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.*

Hardcopy VASI collected off-station was brought back to the VA by approved study personnel who have approved ATT's. This includes MEG/MRI safety screening, Neurofeedback questionnaire (performed directly before Neurofeedback intervention), and payment forms (signed directly after intervention sessions and imaging sessions), were transported back to the VA in a locked briefcase the same day and stored in the investigator's laboratory in 13-407 or 13-404, in the VMRF building.

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.

All hardcopy data, such as coded neuropsychological testing and MHA interviews, will be stored in locked cabinets at Dr. Huang's office at VMRF, 13-407.

Hardcopy VASI, in the form of identifier cards, will be kept in a separate locked cabinet and stored at Dr. Huang's office, in a locked cabinet, in 13-407, in the VMRF building as well as on a secure database on Dr. Huang's R:/drive.

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.

Since all of our electronic study records contain subject I.D. This is considered sensitive data. Therefore, none of our electronic study records are non-sensitive.

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".

Electronic records with VASI is the the electronic code key that will have the participant's name and subject ID and will be kept on Dr. Huang's R:/drive: \\R01SDCHSM02.R01.MED.VA.GOV\Research\Huang\IASIS_MEG_H170033

Coded MEG Data, in .fif files, are stored on a Linux workstation, EE112983, located in 13-406. This workstation is the computer on the right-side of the office. In addition, the coded MEG Data is in the process of being copied onto the VA Cloud, with assistance from Dr. Alan Simmons.

In addition, the MRI data which includes the subject ID, is stored on DVD's at the PI's office in a locked cabinet in 13-407.

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 requred 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.

For hardcopy VASI stored in the VA: Hardcopy VASI will be stored in the investigator's laboratory in 13-407 of VMRF in a locked cabinet and will only be destroyed by Dr. Mingxiong Huang, Ph.D., according to an approved

VA records control schedule. Only approved study personnel will have access to this information.

No individual data will be shared with anyone outside the research team and that only aggregate /outcome data will be shared or published.

For electronic but coded data stored in a computer: Study records entered into a computer system will be assigned code numbers and will not be individually identifiable (per VA handbook 1605.1 Appendix B). The key that relates the code numbers to the individuals will be kept in a locked cabinet in the research team's office in 13-407 at the VMRF building and destroyed according to an approved VA records control schedule and will also be kept in Dr. Huang's R: /drive.

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.

			Principal

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

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*