Protocol Title	Feasibility of a Combined Neuromodulation and Yoga Intervention for Veterans with Mild Traumatic Brain Injury and Chronic Pain
Funding Agency or Sponsor	VA ORD
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Contents

1.0 Background

Clinical Problem:

Over 340,000 mild traumatic brain injuries (mTBI) have occurred as a result of the military conflicts in Iraq and Afghanistan[1]. mTBI leads to a host of poor rehabilitation outcomes including impairments in cognition, physical health, and psychological health. These impairments among people with TBI lead to poor quality of life (QOL)[2]. Worsening this clinical picture, the prevalence of chronic pain is estimated to be between 43.1-70% among Veterans with TBI[3]. Recent research by the Chronic Effects of Neurotrauma Consortium (CENC) indicates that mTBI is strongly associated with increased pain intensity and pain interference[4]. While there is a clear need for effective treatments for mTBI and chronic musculoskeletal pain, such treatment options are lacking. Despite clinical practice guidelines (CPG) recommending ***against*** opioid treatment for people with TBI, this patient cohort remains at increased risk of receiving opioid therapy for chronic musculoskeletal pain[5]. Given the ongoing opioid epidemic in the United States, it is very timely to develop alternative, non-pharmacologic treatments for chronic musculoskeletal pain among Veterans with mTBI.

Yoga, Pain, and TBI: Yoga is an activity and mindfulness-based intervention that may be a promising alternative treatment for mTBI and chronic musculoskeletal pain. Yoga classes are generally comprised of breathing exercises, gentle stretching/yoga, and meditation. Evidence suggests that participating in yoga is helpful for individuals who experience chronic musculoskeletal pain. For example, a RCT of yoga conducted in Veterans with chronic low back pain found that participating n yoga led to reduced disability, pain, and opioid use[6]. Further, a systematic review of yoga interventions for chronic low back pain concluded that participating in yoga (compared to non-exercise controls) results in advances in function at 3 and 6 months[7]. Based on this burgeoning evidence, the American College of Physicians Clinical Practice Guideline recommends yoga as a non-pharmacological treatment for chronic low back pain[8].

An adapted yoga program, LoveYourBrain Yoga, was created and tested specifically for TBI. Led by sets of activities recorded in a program manual, LoveYourBrain Yoga is a 6-session group-based yoga intervention that incorporates breathing exercises, yoga, meditation, and psychoeducation. LoveYourBrain Yoga is feasible and acceptable to people with TBI, and preliminary evidence suggests participating in LoveYourBrain Yoga leads to improvements in many outcomes, including QOL, among people with TBI of all severities [9-11]. However, the impact of LoveYourBrain Yoga on pain outcomes in this population is yet to be tested.

TMS, iTBS and Pain: Neuromodulation through transcranial magnetic stimulation (TMS) is a promising non-invasive, non-pharmacological treatment for TBI and chronic pain. A recent systematic review of repetitive TMS (rTMS) for chronic pain[12] and a recent meta-analysis for rTMS for neuropathic pain[13] demonstrated that high frequency rTMS (>1%) applied to the motor cortex (MC) effectively reduces pain. Additionally, high frequency rTMS applied to the left MC of patients with mTBI-related headache resulted in reductions in headache symptoms[14]. Collectively, these studies indicate that high frequency, excitatory rTMS applied to the MC is beneficial for alleviating pain and can be safely and effectively applied to TBI populations.

Intermittent theta burst stimulation (iTBS) is a type of patterned, excitatory rTMS. A practical advantage of iTBS over rTMS is that iTBS protocols are typically 3 min. in length vs. 30 min. with rTMS. Yet, the research on iTBS for pain and TBI treatment is in its infancy. A recent trial of a single session of iTBS applied to the MC among patients with chronic orofacial pain demonstrated significant, yet transient, improvement in self-reported pain[15]. These promising results may be improved with repeated provision of iTBS treatments over time. Furthermore, evidence suggests that iTBS applied to the dorsolateral prefrontal cortex (DLPFC) may

significantly decrease frequency, duration, and severity of migraine headaches[16]. Another RCT conducted among patients with multiple sclerosis and lower spastic paraparesis examined effects of iTBS, high frequency rTMS (20 Hz), and placebo on spasticity. While researchers found that high-frequency rTMS resulted in better short-term outcomes, iTBS resulted in longer-lasting improvements in outcomes[17].

A single case study utilizing iTBS as a potential treatment for TBI has been reported. This study details the case of a 25-year-old man with TBI who underwent 3 weeks of cerebellar iTBS combined with rehabilitation. This patient experienced improvements in balance performance, motor recovery, step length, and walking speed after iTBS [18]. Importantly, this report suggests that iTBS can be used among individuals with TBI.

iTBS Properties Make it Ideal for Combined Treatment: The effects of iTBS stimulation, typically quantified by increased MC excitability can last up to 60 min.[19] Thus, iTBS can induce a window of neuroplasticity, making it ideally suited to magnify the effects of behavioral treatments provided after it. For example, iTBS provided prior to high frequency (10Hz) rTMS to the MC provided greater analgesia than rTMS alone among patients with chronic refractory neuropathic pain (without iTBS priming)[20]. iTBS has also been successfully combined with cognitive-behavioral therapy to promote smoking cessation[21]. Collectively, emerging evidence suggests that iTBS shows promise to prime the brain for combined interventions and may magnify the impacts that these interventions would have when used alone, leading to an improvement in outcomes.

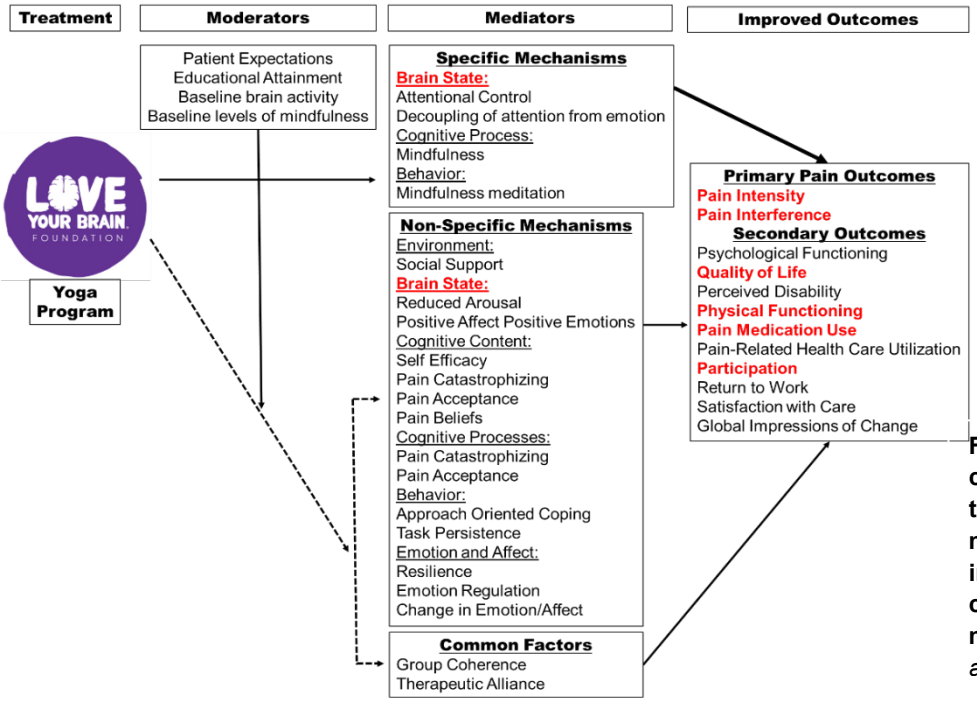

Figure 1. Adapted conceptual model of the mechanisms of mindfulness-based interventions for chronic pain management (Day *et al.* 2014).

*Conceptual Model (**Fig 1**):* Our proposal is guided by Day et al.'s conceptual model of how mindfulness-based interventions are useful for chronic pain management[22]. We chose this model because it is evidence-based and because it incorporates brain state as a specific mechanism/mediator. This is particularly fitting because we hypothesize that iTBS will enhance this brain state to further improve the beneficial effects of the LoveYourBrain yoga program on pain management. This model informed our selection of outcomes, which, for this SPiRE application will include pain intensity, pain interference, QOL, physical functioning, pain medication use, and participation. We will also use this conceptual model to tailor the

psychoeducation provided as part of the LoveYourBrain Yoga program. Psychoeducation will integrate domains identified as non-specific mechanism mediators in the model (e.g., pain acceptance and pain beliefs). The LoveYourBrain Yoga psychoeducation is already focused on resilience, which this model identifies as a non-specific mechanism/mediator as well. Our future RCT building on the results of this SPiRE will investigate moderators and mediators of improved outcomes as a result of participating in iTBS+yoga and will also be guided by this model.

Knowledge Gaps Filled by this SPiRE Project This project will determine how a combined iTBS and the LoveYourBrain Yoga program impacts veterans with mTBI and chronic musculoskeletal pain. First, we will determine if we can combine iTBS with LoveYourBrain Yoga in a manner that is feasible and acceptable. Each of these interventions have been assessed in people with TBI. However, neither of these interventions have been studied among people with mTBI *and chronic musculoskeletal pain*. The preliminary outcome data on chronic musculoskeletal pain, collected in this study, will establish the foundation for determining the merits of continuing the development of iTBS+yoga as a treatment to attenuate mTBI-related chronic musculoskeletal pain and improve function. To advance our understanding of effects of iTBS+yoga, we can also build on the LoveYourBrain foundation data built by our consultant (Donnelly). Specifically, we selected outcomes for this SPiRE to enable comparisons of iTBS+yoga outcomes with the same QOL, feasibility and quantitative acceptability data (i.e., satisfaction rating scale) collected from individuals with mTBI who completed the LoveYourBrain yoga program without iTBS[9-11,23]. Comparing these same outcomes for our prospective iTBS+yoga cohort with the retrospective yoga alone cohort will allow us to determine the potential differential effects of iTBS+yoga on QOL, acceptability and feasibility.

SPiRE Project Knowledge Advancements in Rehabilitation Research This SPiRE project will advance knowledge by determining if combining iTBS and the LoveYourBrain Yoga program is feasible and acceptable to Veterans with mTBI and chronic musculoskeletal pain. If the results are promising, this research will provide critical preliminary data for a VA RR&D Merit/IIR application for an RCT assessing the impacts of iTBS+yoga in a larger sample of Veterans. In addition, this project will provide novel information about the impacts of a combined neuromodulation and yoga program, specifically, whether iTBS can enhance the impacts of subsequent participation in an activity-based intervention (i.e., yoga). If we find that iTBS does, in fact, magnify the impacts of a subsequent intervention, this combinatorial model can be applied to and tested with other interventions (e.g., meditation, exercise) and among other outcomes (e.g., sleep) within rehabilitation populations, as well.

Significance of the Research and How it Relates to RR&D Priority Areas This SPiRE aligns with the mission of RR&D to maximize functional recovery and has clearly evident potential for translation to clinical rehabilitation. This SPiRE project includes aims that address non-pharmacological activity-based interventions for chronic musculoskeletal pain impacting outcomes that include pain reduction, medication use, function, and QOL.

Importance and Health Relevance By demonstrating the feasibility and acceptability of iTBS+yoga, we will be a step closer to providing a novel, non-pharmacologic treatment for Veterans with mTBI and chronic musculoskeletal pain. If the SPiRE aims are achieved, the effectiveness of iTBS and LoveYourBrain Yoga can be further explored. Achieving the SPiRE aims are essential first steps towards carrying out a large-scale RCT to test for treatment efficacy. This will represent great progress for the 43-70% of Veterans with TBI[3] who live with chronic pain.

Direct Benefit to Veterans and VA Services This SPiRE project will directly benefit Veterans and VA Services by developing a new, non-pharmacological neurorehabilitation treatment for Veterans with mTBI and chronic musculoskeletal pain in need of non-opioid treatment options or who do not find existing options to be effective or preferable. If efficacious, our proposed iTBS+yoga intervention is primed for diffusion across the VA system of care. TMS is now offered at 30 VA hospitals nationwide for depression, and yoga is among the complementary and integrative health (CIH) programs being rolled out as a part of the VAs nation-wide Whole Health implementation efforts[24], with classes offered through VA services such as recreational therapy. Thus, should iTBS+yoga ultimately proves to be efficacious and effective, VA facilities will be well-poised to offer this treatment.

2.0 Testable Hypotheses

Recent evidence suggests that non-invasive neuromodulation through repetitive transcranial magnetic stimulation (rTMS) is a promising non-pharmacological treatment for chronic musculoskeletal pain. Specifically, high frequency rTMS applied to the motor cortex (MC) reduces pain among people with chronic and neuropathic pain[12,13]. A type of patterned, excitatory rTMS, called intermittent theta burst stimulation (iTBS), is thought to be particularly promising as it can increase excitability of the MC[19] that lasts after the cessation of iTBS. This time-period of post-iTBS enhanced MC excitability makes iTBS ideally suited to magnify the effects of behavioral treatments. More specifically, iTBS shows promise to prime the brain to magnify the impacts and benefits of interventions provided during this time-period of enhanced MC excitability[20,21]. Yoga is an activity and mindfulness-based behavioral intervention ideally suited for this purpose.

In this study, we will test the idea that for mTBI-related chronic musculoskeletal pain the beneficial effects of yoga can be magnified if it is provided immediately after provision of iTBS (iTBS+yoga). LoveYourBrain Yoga is an adapted yoga program that was created and tested specifically for people with TBI. LoveYourBrain Yoga is a 6-session, manualized, group-based yoga intervention incorporating breathing exercises, yoga, meditation, and psychoeducation. LoveYourBrain Yoga is feasible and acceptable to people with TBI, and evidence suggests participating in LoveYourBrain Yoga leads to improvements in outcomes including QOL among people with TBI of all severities[9-11]. However, effects of LoveYourBrain Yoga on pain outcomes among Veterans with mTBI and chronic musculoskeletal pain are yet to be tested.

Our long-term goal is to demonstrate efficacy of iTBS+yoga on improving QOL, function, and pain among Veterans with mTBI and chronic musculoskeletal pain. The objectives of this pilot study, essential first steps towards this goal, are to develop a combined iTBS+yoga intervention, assess the intervention's feasibility and acceptability, and to gather preliminary clinical outcome data on QOL, function and pain that will guide future studies.

Our central hypothesis is that our combined iTBS+yoga intervention will be feasible and acceptable for Veterans with mTBI and chronic musculoskeletal pain. This hypothesis is based on existing literature and our preliminary data demonstrating that iTBS[18] and the LoveYourBrain yoga program[9], provided separately, are each feasible and acceptable among people with TBI.

We will address these objectives and hypothesis with the following specific aims conducted in a single group, within subject design wherein all 20 Veterans with mTBI and chronic musculoskeletal pain will receive iTBS+yoga:

3.0 Specific Aims

Aim 1: Develop a novel, combined iTBS+yoga neurorehabilitation intervention for Veterans with mTBI and chronic musculoskeletal pain. The intervention will combine iTBS treatment (3min), which will be provided prior to the established LoveYourBrain Yoga program (90min). iTBS+yoga treatment sessions will be conducted once a week for 6-weeks. We will finalize logistics for combining iTBS with LoveYourBrain Yoga and offering it to Veterans with mTBI and chronic musculoskeletal pain. This will include determining how many participants can be accommodated in small group sessions, tailoring the psychoeducation of the yoga component, and other safety and logistical considerations.

Aim 2: Examine the feasibility and acceptability of iTBS+yoga for Veterans with mTBI and chronic musculoskeletal pain. All Veterans (N=20) will receive 6 weekly sessions of iTBS+yoga. We hypothesize that iTBS+yoga will be feasible as indicated by Veteran's initiation and completion of all 6 weeks of the intervention. Acceptability will be assessed quantitatively through satisfaction ratings and qualitatively using semi-structured interviews.

Aim 3: Establish the foundation for sample size and power considerations for a future clinical trial to examine the effectiveness of iTBS+yoga on Veterans' QOL, function and pain outcomes. This will be achieved by collecting preliminary data of Veterans self-reported QOL, function and pain outcomes before (baseline) and after (endpoint) the 6-week iTBS+yoga intervention.

4.0 Study Design and Methods

The proposed research involves human subjects and will NOT involve animals.
Design: Prospective within-subject pilot study to develop iTBS+yoga intervention, examine the feasibility and acceptability of 6 sessions of iTBS+yoga over 6 weeks, and gather preliminary data on pain, function and QOL.

Veteran Sample: Twenty Veterans above the age of 22 with mTBI and chronic musculoskeletal pain will be included. Veteran participants must perceive themselves as able to participate in gentle physical movements and will be cleared for gentle exercise by a study team physician. mTBI will be defined according to the VA/DoD CPG[25] utilizing the mTBI symptom attribution and classification algorithm (SACA)[26]. Chronic musculoskeletal pain will be operationally defined as pain in the muscles, bones, ligaments, tendons and/or nerves that persists for >6 months and is of moderate to severe intensity as indicated by a score of >5 on specific items on the Brief Pain Inventory (BPI)[27]. For safety, we will exclude persons with contraindications to TMS or MRI. Detailed eligibility criteria are provided in **Table 1**. We will include both males and females. We *will not exclude* participants based on gender, ethnicity or race. Subjects with major depressive disorder and other psychological disorders *will not be excluded* and these diagnoses will be documented as potential covariates.

Participant Recruitment Plan: We will recruit Veterans from the TBI/Polytrauma program at Edward Hines Jr., VA Hospital (Hines VA). TBI/Polytrauma program personnel will inform TBI/Polytrauma program members about the study through routine staff meetings. The PI will also present updates on this study on a quarterly basis. Dr. Herrold and research team members will be added as Co-Signers in the electronic medical record of TBI/Polytrauma patients that may be a good fit for this study. Research team members will then be able to

screen these for eligibility and send eligible Veterans an informational letter about the study. Research team members will then make follow-up screening phone calls.

We will also mail informational letters to Veterans who have completed our past studies and permitted us to contact them about future studies through a TBI Data Repository (Hines IRB#14-003, Co-PIs Herrold & Pape) created for recruitment purposes. This repository currently includes over 300 Veterans and continues to grow with ongoing studies.

Table 1. Participant Eligibility Criteria
Inclusion Criteria
• 22+ years of age • Can read and speak English • Perceive themselves as able to participate in gentle physical movements and cleared by study physician to do so. • mTBI Criteria: Symptom Attribution and Classification (SACA) criteria for mTBI (without requirement of clinical neuropsychological impairment) • Chronic musculoskeletal pain: pain (in muscles, bones, ligaments, tendons and/or nerves) that persists for >6 months and is of moderate to severe intensity with a score of >5 on specific items on the Brief Pain Inventory (BPI) • Fully vaccinated against COVID-19 prior to study participation
Exclusion Criteria
• Contraindications to iTBS/TMS (e.g. epilepsy, history of anoxic brain injury or heart disease) • Contraindications to MRI (e.g., claustrophobia, ferromagnetic metal implants) • Pain believed to be associated with cardiac or ischemic conditions • Active seizure disorder, or if they are taking psychostimulants (e.g. amphetamines), anticholinergics or other medications that may increase their risk of having seizures. • History of moderate to severe TBI • History of or current psychosis not due to an external cause (e.g., due to illicit drug use) • Are pregnant or nursing • Within 12 weeks of a major surgery/operation • Have questionably valid test profiles

Recruitment Feasibility at Hines VA Recruitment Site: In 2019 at Hines VA there were 1,737 unique Veteran patients with ICD-10 diagnostic codes for mTBI or chronic musculoskeletal pain within the TBI/Polytrauma program. Given that chronic pain co-occurs 43-70% among Veterans with TBI[3], we conservatively estimate that 694 (40% of 1,737) unique Veterans who received TBI/Polytrauma services in 2019 alone would meet study eligibility criteria. Thus, enrolling 10 Veterans a year for 2 years for this SPiRE project is quite feasible.

Initial Eligibility Screening: A partial HIPAA waiver and waiver of informed consent for screening purposes will provide regulatory approval to screen candidates to determine study eligibility prior to obtaining informed consent. Veterans identified as research candidates will

complete an initial phone screening for the following: (1) probable mTBI, using the Ohio State University TBI Identification Method (a TBI Common Data Element, CDE)[28], (2) MRI safety, using the Hines VA safety form, and (3) self-reported age and ability to read and speak English. (4) Age will be verified in the EMR (i.e., CPRS or CAPRI). (5) A list of prescribed and over-the counter medications and the length of time the participant has been on each medication will also be collected over the telephone. Current medications will be cross-referenced with study eligibility criteria and the EMR to identify any antiepileptics, and any medications known to lower seizure threshold. The electronic medical record (EMR) will also be reviewed for study eligibility criteria. In response to the global SARS-CoV-2 (COVID-19) pandemic, documentation of full COVID-19 vaccination will be confirmed. If review findings indicate possible contraindications to rTMS or MRI related to a metal implant, then the model and manufacturer of the implant will be obtained to determine whether or not it is safe to expose the implant to a strong magnet. Manufacturer recommendations regarding safety will be followed. If potential participants meet all eligibility criteria, they will be scheduled for the first research visit. They will be mailed a copy of the informed consent form to review, and an appointment reminder of the appointment date and time.

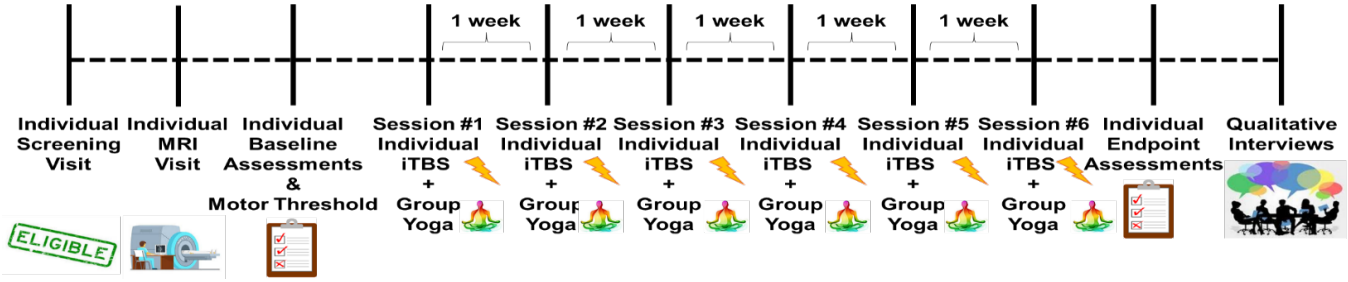

Figure 3. Study Timeline

5.0 Research and Data Collection Procedures (Fig 3):

Due to the COVID-19 pandemic, the PI may elect to increase social distancing measures and utilize telehealth to complete portions of the protocol via phone or VA-approved telehealth technologies.

Informed Consent: Authorized clinical researchers will meet eligible participants at a designated entrance, closest in proximity to a private room, where the study visit is to take place. The researcher will provide all documentation, to include the study consent form and all assessments the participant will need to complete. All participants will be able to make their own decisions regarding research participation. They will be encouraged to discuss the study with a family member or friend before agreeing to participate. The participant will not be openly encouraged to participate in the research or told that there is any expected benefit from the experimental interventions during participation. Research participants will have access to research staff to assist with any questions or concerns until understanding is achieved to the judgement of the individual asking the question. If a participant refuses participation, no further contact will be made. If signed informed consent forms are completed, a note will be made in the Hines VA EMR, and the original consent will be kept in a locked cabinet in a locked research office behind swipe-access doors in Bldg. 1, Room B-351 or B-318 of Hines VA. Copies of the

signed consent forms will be provided to the Hines VA IRB Office. Additionally, a copy will be provided to the participant. After informed consent processes are concluded, participants will complete a saliva alcohol test, a urine drug screen and pregnancy test for females to confirm eligibility.

Consent documents will be stored in locked file cabinet, behind a locked door at the Hines VA Bldg. 1, Room B-351 or B-318.

Drug and Alcohol Screening: Abstinence from alcohol and illicit substances will be requested for each visit and will be confirmed with a saliva alcohol test and urine drug screen (breathalyzer testing will not be utilized at this time due to aerosolization concerns – in compliance with COVID-19 safety precautions). On Visit 1, the urine drug screen will be completed by Hines VA clinical laboratory using a manual requisition with the participant's unique subject ID number. All

Table 2. Study Assessments

Assessment Name	Assessment Purpose
Screening Assessments:	
Structured Diagnostic Interview (STDI)[138] with the Neurobehavioral Symptom Inventory (NSI, TBI-CDE)[141]	mTBI eligibility
California Verbal Learning Test-II (CVLT-II)[142]	Memory and performance effort validity
Minnesota Multiphasic Personality Inventory-2-RF (MMPI-2-RF)[144]	Symptom reporting validity
Brief Pain Inventory (BPI) [139]	Preliminary pain data & eligibility
Hines VA MRI Safety Form and TMS Safety Form	MRI & TMS safety compatibility
Demographics	Sample characterization
Baseline and Endpoint Assessments for Study Outcomes:	
TBI-QOL (TBI-CDE)	Preliminary quality of life data
Mayo-Portland Adaptability Index (TBI-CDE)	Preliminary function and participation data
Pain Interference scale (PROMIS)	Preliminary pain data
Therapy Activity Data Collection	Preliminary Therapeutic Activity data
Session completion rates	Feasibility (Endpoint only)
Structured qualitative interviews	Acceptability (Endpoint only)
Satisfaction ratings	Acceptability (Endpoint only)
Home & community yoga & meditation diaries	Covariate (each weekly session)

subsequent urine drug screens will be conducted using a urine test kit by research staff. No results from the urine drug screen will be entered into the Veteran participant's medical record. These results will be for research purposes only. Any participant testing positive for alcohol, or illicit drugs (with the exception of prescribed opiates) will be asked to re-schedule research procedures, and safe transportation will be arranged (e.g., taxi) or participants will be escorted to the ER or mental health intake as appropriate.

All female participants will complete a pregnancy test during the Visit 1 screening visit. If a pregnancy test is positive, then participation in the study will stop.

Table 2 Summarizes assessments conducted during the study.

Visit 1 (Individual Screening Visit):

Pre-visit / Post-visit screening: Authorized clinical researchers will contact study participants to review procedures for accessing Hines VA facility prior to the scheduled study visit date. Research staff will complete a COVID-19 screening questionnaire with the participant over the phone 1 day prior to the visit date.

Potential participants will first complete a finite set of assessments from the mTBI SACA (Pape, Herrold *et al.* 2016)[138]. The Structured Diagnostic Interview (STDI), included in the SACA, will be used to establish the mTBI history including duration of loss of consciousness (LOC), alteration of consciousness (AOC), and post-traumatic amnesia (PTA)[138]. The Brief Pain Inventory (Short Form) will be used to identify and confirm inclusion criteria related to participant's reports of musculoskeletal pain. The interview ends with the Neurobehavioral Symptom Inventory [NSI, a TBI Common Data Element (CDE)[141]]. The California Verbal Learning Test-II (CVLT-II)[142] will be used to assess verbal memory, a cognitive domain affected by mTBI. To determine validity of test profiles, the CVLT-II forced choice component will be used, with a cutoff score of 15, as a measure of effort performance[143]. To determine validity of symptom reporting, the Minnesota Multiphasic Personality Inventory-2-RF (MMPI-2-RF)[144] will be used to identify abnormal symptom reporting via this criteria: F: T score ≥ 107; F(p): T score ≥ 85; TRIN: T score ≥ 80; VRIN: T score ≥ 80)[138].

During the screening process, a study physician will evaluate the Veteran's ability to engage in gentle exercise and their pain management strategy including OTC analgesics that they might take during the intervention. On the screening visit the participant will be instructed to bring in all medications with them to complete the Medication Inventory including OTC analgesics. We will also screen the electronic medical record for medical history criteria. Participants will still be able to receive other potential treatments to assist with the management of chronic musculoskeletal pain. These pain management strategies/treatments must remain stable during study participation. Other treatments for chronic musculoskeletal pain that the participant's provider may discuss with them could include physical therapy, occupational therapy, chiropractic care, acupuncture, injections (steroid, prolotherapy, trigger point injections) if these are appropriate. Participants will remain on their usual pain medications while participating in the study. Upon the initial evaluation, all medication dosage and frequency will be documented. All subjects will have their medication dosage and frequency documented at the completion of

the study.

Once the study visit is completed, authorized clinical researchers will complete a follow up phone call with each participant, which will include completion of an additional COVID-19 screening form.

Visit 2 (Individual MRI): A high-resolution, structural MRI scan will be collected in order to allow for iTBS treatment site neuronavigation for each participant. The MRI will take place at Hines VAH and this visit will last approximately 30 minutes.

All established COVID-19 safety precautions will be followed, as identified by Edward Hines Jr. VA Hospital administration.

MRI Scan

- Participant will also undergo a **magnetic resonance imaging scan (MRI)** to look at the brain. An MRI is a type of scan that uses magnetic fields and radio waves to take a picture of the brain. The MRI will last about 15 minutes.

In order to make sure the MRI procedure will be safe; participant will be asked to fill out a screening form before starting the study. It is important that participants tell the researchers in this study if they have any history of:

- Metal fragments in the eyes or face.
- Implantation of any electronic devices such as (but not limited to) cardiac pacemakers, cardiac defibrillators, cochlea implants or nerve stimulators.
- Surgery on the blood vessels of the brain or the valves of the heart
- Claustrophobia (fear of enclosed places)
- Body piercing or tattoos

Participants will be asked to change into a hospital gown or surgical scrubs and remove any metal, such as earrings.

An MRI technician will give participants instructions outside the MRI scanner about the scanning. Next, participants will be asked to lie still on the MRI patient table and their heads will be placed in a specially designed head holder. The participant's head will be cushioned by a firm foam pillow. The table will then slide into the enclosed space of the MRI scanner.

The information from the MRI scanner is only useful if participants are able to complete the whole imaging session and hold their heads very still the whole time. Therefore, participant will be encouraged to hold as still as possible, and to let the investigators know if they are uncomfortable in any way as soon as possible after the imaging session begins.

The front of the head-holder will be open, which lets participants look through a special mirror and see pictures presented to them on a projection screen near their feet. Sounds may also be

presented to participants using specially designed headphones. Participants will be asked to hold their heads as still as possible and to respond to the pictures or sounds by pushing a button or thinking quietly to themselves.

The MRI scanner makes loud banging noises while taking a measurement, so either ear plugs or specially designed headphones will be used to reduce the noise. The researchers will be in communication with the participant through an intercom system to tell them how the study is going. The earplugs or headphones should not get in the way of communicating with the researchers. Participant can speak to the technician by talking out loud. If at any time or for any reason, participants wish to stop the exam, they may do so by squeezing a rubber ball. This will signal the MRI technician to stop the scanner.

The MRI pictures in this study will be reviewed by a neuroradiologist. If an abnormality is detected during the processing of the scan, participants will be contacted, and the information will be provided. Participants will be asked to provide us with the name and address of the provider of their choice. Appropriate Release of Information documentation and processes will be used to transport the records. Participants will be encouraged to schedule a visit with their provider for appropriate medical advice.

Visit 3 (Individual Baseline & Motor Threshold): Individual baseline assessments will be completed during this study visit. These will include self-report questionnaires about TBI-related quality of life (TBI-QOL), function (Mayo Portland Adaptability Index) and pain (Pain Interference Scale). Participants will also be instructed to keep diaries of utilization of pain medication and other pain management strategies. Participants will also complete weekly diaries detailing the time they spent at home or in the community engaging in meditation or yoga practices.

Individual Motor Threshold (MT): Each participant's T1 MRI, will be loaded into a Localite TMS Neural Navigator system. A MagVenture C-B60 coil will be used to deliver single pulse TMS to the non-dominant MC to identify the abductor pollicis brevis (APB) muscle coordinates. Stimulation intensity that will be used in iTBS will be determined by collecting each participant's motor threshold (MT) using the finger representations of the motor cortex. The consensus in the literature is that iTBS can be safely provided at 80% of active motor threshold (AMT). Since there is more within and between subject variability with AMT (e.g, different gripping strengths), relative to resting motor threshold (RMT), scientifically the RMT is preferred. There is also recent evidence that motor threshold estimates using RMT and AMT are equivalent.[201] This means that treatment intensity, based on these two MT estimation procedures, would be equivalent, we will use RMT to estimate MT and compute treatment intensity. RMT will be defined as the lowest stimulus intensity necessary to produce motor-evoked potentials (MEPs) ≥50μV in 5/10 trials. Thus, the standard iTBS parameters will be used in this trial to maximize safety. iTBS will be provided at 80% of RMT.

The electrodes used in this process will be placed using a gel or sticky paste.

The test will take about **1 hour**.

Visits 4-9 (iTBS+Yoga Treatment Sessions): iTBS+Yoga sessions will occur once a week for 6 weeks. These sessions will occur at Hines VAH, with only essential research staff present, and take approximately 1.5 hours. Each session will start with individual iTBS (3 min.). Then,

small group yoga sessions will occur. All reasonable precautions will be made to prevent contact with/spread of SARS COV-19, per Hines Hospital policy.

Because of potential pain (see POSSIBLE RISKS OR DISCOMFORTS below), we recommend that participants bring an over the counter pain reliever of their choice to take prior to each iTBS session. We will ask participants when they took the medication and the amount.

Pre-iTBS Assessments:

- Participants will be asked to complete a saliva alcohol test to help the research team determine the amount of alcohol that may be in the participant's bloodstream. During this alcohol screening, participant will be asked to blow into a tube attached to a special hand-held machine. No results will be entered into participant's electronic medical record.

- Participants will be asked to provide a urine sample to allow the research team to determine if certain drugs are in participant's body. This includes pain medications like morphine and Vicodin; benzodiazepines such as Valium, Librium, Xanax and Ativan, that are usually used to treat anxiety or alcohol withdrawal; and substances like cocaine, marijuana/cannabis, heroin, amphetamine or speed and barbiturates.

It is important to know that any alcohol tests or urine drug screening results are used to determine if participants are eligible to continue in this research study and will **NOT** be entered into participant's medical record or reported to legal authorities.

Intermittent Theta Burst Stimulation (iTBS) Treatment Sessions:

Neuromodulation through transcranial magnetic stimulation (TMS) is a promising non-invasive, non-pharmacological treatment for TBI and chronic musculoskeletal pain. A recent systematic review of repetitive TMS (rTMS) for chronic pain[6] and a recent meta-analysis for rTMS for neuropathic pain[7] demonstrated that high frequency rTMS (>1%) applied to the motor cortex (MC) effectively reduces pain. Additionally, high frequency rTMS applied to the left MC of patients with mTBI-related headache resulted in reductions in headache symptoms[18]. Collectively, these studies indicate that high frequency, excitatory rTMS applied to the MC is beneficial for alleviating pain and can be safely and effectively applied to TBI populations.

iTBS Properties Make it Ideal for Combined Treatment: The effects of iTBS stimulation, typically quantified by increased MC excitability can last up to 60 min.[8] Thus, iTBS can induce a window of neuroplasticity, making it ideally suited to magnify the effects of behavioral treatments provided after it. For example, iTBS provided prior to high frequency (10Hz) rTMS to the MC provided greater analgesia than rTMS alone among patients with chronic refractory neuropathic pain (without iTBS priming)[9]. iTBS has also been successfully combined with cognitive-behavioral therapy to promote smoking cessation[10]. Collectively, emerging evidence suggests that iTBS shows promise to prime the brain for combined interventions and may magnify the impacts that these interventions would have when used alone, leading to an improvement in outcomes.

iTBS+Yoga Intervention: Intervention sessions will occur once a week for 6 weeks. Each session will start with individual iTBS (3 min.). We will use the T1 MRI to localize the stimulation site, which will be each participant's dominant trunk representation area of the MC. iTBS will be delivered utilizing the MagVentrure Mag-Pro X100 with MagOption stimulator that includes

active and placebo coils (C-B60 Butterfly coils). Only the active setting will be used. iTBS parameters include 3 pulses of stimulation given at 50Hz, repeated every 200ms at 80% of the resting MT18. The inter-pulse-interval is 20ms. A 2s train of TBS, is repeated every 10s for a total of 190s, which equates to a total of 600 pulses[32].

During the iTBS treatments, ear buds will be placed in subject's ears because the magnetic stimulator makes a loud clicking noise. Tape may be placed over the ear buds to make sure the ear buds stay in place.

Each complete session will take about 15 minutes to allow for set-up and take-down. Appropriate surfaces will be sanitized before and after each study participant. The weekly schedule for iTBS will be one session of iTBS every week (on the same weekday and time if possible) for 6 weeks. In order to monitor for safety, all iTBS sessions will be videotaped. All security procedures for data will apply. Acknowledgement for picture and video will be completed as part of HIPAA Authorization documentation. A total of 6 iTBS sessions will be provided over six weeks.

Love Your Brain Yoga Sessions: After the iTBS sessions, participant will complete a small group (approximately 3-6 people) yoga session. Each yoga session includes 10 minutes of breathing exercises, 45 minutes of gentle yoga/stretching, 15 minutes of guided meditation, and 20 minutes of facilitated discussion with psychoeducation.

Safety Measures: Subjects will participate in safety monitoring using the Data Safety Monitoring Scale (DSMS). This scale rates changes from baseline vital signs (temperature, blood pressure, heart rate, oxygen saturation levels), fatigue, tinnitus (ringing in the ears), sleep, dizziness, nausea, vomiting, confusion, seizure, syncope (fainting), headache, neck pain, skin integrity of the scalp, and substance use.

Visit 10 (Endpoint Assessments): Individual endpoint assessments will be completed during this study visit. These will include repeating self-report questionnaires about TBI-related quality of life (TBI-QOL), function (Mayo Portland Adaptability Index) and pain (Brief Pain Inventory and Pain Interference Scale). Additionally, we will ask participants to complete satisfaction ratings of the iTBS+Yoga sessions and to turn in participants' pain management and yoga/meditiatation diaries.

Visit 11 (Qualitative Interviews): Participants will be asked to take part in semi-structured interviews that will be audio-recorded. Interviews will elicit feedback about Veteran experiences with iTBS+yoga intervention participation, barriers and facilitators to participation, perceptions of the intervention, how participation may have impacted key pain-related outcomes and quality of life, and suggestions for improvement.

Study Outcomes – Individual Baseline & Endpoint Assessments: Feasibility will be defined by enrollment and the number of sessions completed by each participant. Acceptability will be quantitatively assessed using satisfaction ratings[9] and qualitatively assessed *via* semi-structured interviews with all study participants. Interviews will elicit feedback about Veteran experiences with intervention participation, barriers and facilitators to participation, perceptions of the intervention, how participation may have impacted key pain-related outcomes and their QOL, and suggestions for improvement. TBI CDE outcomes will include: the TBI-QOL scale and

Mayo-Portland Adaptability Index.

The Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference scale and the BPI will also be used, along with utilization of pain medication and other pain management strategies collected via self-report and chart review. Participants will also complete weekly diaries detailing the time they spent at home or in the community engaging in meditation or yoga practices, which will be used as a potential covariate in analyses.

5.1 Possible Risks or Discomforts

Intermittent Theta Burst Stimulation (iTBS - TMS) The biggest concern for magnetic stimulation is seizure induction. Other known side effects of iTBS include headache, dizziness, tinnitus, nausea, neck pain or scalp burns (Rossi et al, 2009)[32]. Alcohol use and alcohol withdrawal may introduce an unknown seizure risk as both of these circumstances lower the seizure threshold[32]. For this reason, any participant with a positive saliva alcohol test result will not be stimulated and iTBS will be re-scheduled.

Additional Known risks are:

- Possible electrocution during iTBS due to insufficient insulation of the coil. The coils will be inspected before and after each iTBS session to ensure that the coil does not have any cracks or loss of integrity.
- Physical discomfort, facial numbness, headache or dental pain. Mechanical vibrations that occur within the coil while a TMS pulse is being generated, for example, may result in discomfort or headache
- Device failure due to overheating, electrical short-circuiting or mechanical breakdown from force on the device. All precautions will be taken to prevent device breakdown that may affect the welfare of the participant. The TMS device will be inspected routinely and safety guidelines from the manufacturer will be followed.
- Contamination transferred from one participant to another following treatment. The device will be disinfected after every use to prevent spread of germs between participants.
- Mania, depression, anxiety and suicidality, although rare and usually associated with depression or bipolar depression. Repeat measures are collected to monitor for emergence of new mental health conditions and worsening of existing conditions. If new conditions emerge or existing conditions worsen, then the participant will be withdrawn and follow up with their established care team will be recommended.

Behavioral Assessments: The participant may experience some distress when completing behavioral assessments. The participant will be asked to notify study staff if these questions or questionnaires make them feel uncomfortable in order to make sure that the participant has timely access to mental health resources or information for organizations they can contact for support. Participants will be questioned about mTBI symptoms, and circumstances related to chronic musculoskeletal pain they are experiencing, routinely during study participation. Safety management of adverse responses to these measures is outlined below.

Neuroimaging: There are no known risks associated with the MRI procedures, although some participants experience mild discomfort from trying to keep still during the MRI, and some participants feel anxious or claustrophobic in the scanner. This is minimized by having the researchers in constant communication (via headphones) with the participant.

Unknown TMS Risks: There may be other unknown and/or unanticipated side effects that could occur. An adverse events (AE) log and daily study monitor log will be used to monitor the occurrence of any AE including unanticipated events (A response plan to unanticipated AE in delineated in section 11.0 Monitoring and Reporting Serious Adverse Events).

Confidentiality: Loss of confidentiality is a potential risk. This research study involves collection of self-report measures. Participant's responses to self-report questionnaires will be documented. To protect confidentiality, all hard copies of questionnaires and behavioral assessments as well as urine screens and saliva alcohol test screens will be assigned a unique participant identification number and the date the assessment was completed.

Precautions Taken to Minimize Risks:

iTBS Safety Monitoring: The iTBS (TMS) Safety Sheet (DSMS) contains a customized severity indicator scale. Additionally, an Adverse Events Tracking Log has been developed for this project. Both are integrated into the safety monitoring of this study. All serious and non-serious adverse events will be tracked on the Adverse Event Tracking Log.

For each safety variable specified on the DSMS, change from baseline is rated according to severity and for each severity rating there is a specified medical response to be followed. The ratings are on a scale of 1 to 5 with a higher number indicating more deleterious change. This scale rates changes from baseline in vital signs (temperature, blood pressure, heart rate, oxygen saturation levels), fatigue, tinnitus, sleep, dizziness, nausea, vomiting, confusion, seizure, syncope (fainting), headache, neck pain, skin integrity of the scalp, substance use, and PTSD symptoms. This scale will be completed at baseline and then weekly thereafter.

Participants will be clinically monitored for seizure by trained research staff. Should a seizure occur, the following response plan would occur:

1) Research team member to activate emergency code for Hines RRT
2) Other research team member to call 911.
3) Trained research staff to assess airway, breathing and circulation (ABC)
4) When RRT arrives, their staff will take over, assess and treat the participant if needed
5) RRT emergency team will transport participant to Hines ED
    a. For participants treated at Hines VA ED, the PI will contact the participant within a week and encourage them to follow-up with their Primary Care Physician (it is Hines VA policy that patients treated in the ED follow up with their Primary Care Physician within 2 weeks).
6) As outlined below, any seizure will result in stopping treatment and withdrawal from study.

All female participants will complete a pregnancy test during study participation. If a pregnancy test is positive, then participation in the study will stop.

Before receiving treatment, participants will meet with a study team physician to review their pain medications, pain management strategies and to determine whether or not it is safe to participate in gentle physical movements. Participants may be advised to take a pain reliever of their choice (i.e. Acetaminophen /Tylenol) prior to iTBS sessions if discomfort is anticipated.

If, in the opinion of the PI, you are no longer appropriate for the study, you may be discontinued without regard to your wishes to remain, in order to ensure your safety. This would apply if you

do not comply with the requirements for participation, if it becomes medically unsafe for you to continue, if the study is stopped by a sponsor, or if the Department of Health and Human Services withdraws approval.

LoveYourBrain Yoga Program: As with any exercise program, there is a risk of pain or muscle soreness due to increased physical activity. There is also a low risk of falling due to the physical activity and balance challenges involved in the yoga group. To minimize the risk of unnecessary increases in pain or muscle soreness or falls, you will work with trained researchers and clinicians certified in the LoveYourBrain Yoga program. You will have an opportunity to rest and you will be monitored for verbal or visual signs of fatigue or discomfort.

Because psychological symptoms might surface or get worse during the discussion portion of the LoveYourBrain Yoga program, you will be monitored for changes in psychological symptoms and will be offered resources and follow-up care if needed (i.e. psychological support/follow-up, support groups, etc.).

Structural MRI: There are no known risks associated with MRI, although some people have experienced discomfort in trying to remain still. The MRI scanner makes loud banging noises while taking a measurement, so earplugs will be used to reduce the noise. The researchers will be in communication with you through an intercom system to ask how you are doing. The earplugs should not get in the way of communicating with the researchers. You can speak to the technician just by talking out loud. If at any time or for any reason, you wish to stop the exam, you may do so by squeezing a rubber ball we provide. Some people have been noted to be anxious or claustrophobic during the scan.

Psychological: During the study visits, you will complete self-report measures and structured interviews related to mTBI, quality of life, pain, and functioning. You may experience distress in speaking about these sensitive topics. You will be asked to notify study staff if these questions or questionnaires make you feel uncomfortable. If needed, research staff will make sure you have timely access to mental health resources or information on organizations to contact for support. If you express extreme distress while completing these assessments, research staff will stop the interview.

Loss of confidentiality: Loss of confidentiality is a potential risk. You will complete questionnaires that discuss mental health symptoms, disability, mTBI symptoms. All of your responses will be documented.***:*** To protect you from a breach of confidentiality, you will be assigned a unique identification number by the study personnel. This number will be placed on all hard forms, and kept in a locked file cabinet in a locked office at Hines VA. Any specimens you provide will also be marked with this identification number and the collection date to guard against privacy risk. The consent and HIPAA documents you sign will contain protected information (i.e., Name, social security number, etc.). To keep them safe, these documents will be stored in a different area from the rest of the study rooms, but still in a locked file cabinet inside a locked office at Hines VA. All electronic data will be entered in an electronic database on the Hines VA secure server.

MRI data will be de-identified and uploaded to a VA secure server.

Because this is a new use for the iTBS device, we do not know all of its negative effects; and it cannot be guaranteed that you will be able to continue receiving this treatment after this study is over.

5.2 Withdrawal of Subjects

Study participation is voluntary. However, if the participant withdraws or the PI withdraws the participant from the study, the participant will receive a prorated amount based on how much of the study they completed. The participant will be reimbursed in cash from the agent cashier's office at Hines VA. No existing benefits or services will be lost as a result of study withdrawal.

Any seizure will result in stopping treatment and withdrawal from the study. The Hines Ready Response Team will be contacted for emergency assistance, and the participant will be advised to follow up with their established healthcare provider.

If new conditions emerge or existing conditions worsen, then the participant will be withdrawn. The participant will receive pro-rated compensation for the portion of the study they have completed.

Participants will still be able to receive their ongoing treatments to assist with the management of existing chronic musculoskeletal pain. We will encourage participants to work with their provider on pain management strategies. While we require participants to adhere to a stable pain management strategy while in the study, other treatments for their chronic musculoskeletal pain that a provider may discuss with them could include physical therapy, occupational therapy, chiropractic care, acupuncture, injections (steroid, prolotherapy, trigger point injections) if these are appropriate.

6.0 Benefits of Participation in the Study

The participants may not, themselves, benefit from participation in the first and third aims of the research study. However, the Veteran population as a whole will potentially benefit from findings acquired in the research study. It is expected that by receiving iTBS and the LoveYourBrain Yoga program, participants may benefit by experiencing an improvement in quality of life and/or chronic musculoskeletal pain.

7.0 Compensation

Each participant is eligible to receive up to $190 for participation this payment. This compensation is intended to facilitate participation without adding undue influence. If the participant withdraws or the PI withdraws them from the study, the participant will receive a prorated amount based on how much of the study they completed. Participants are eligible to receive $50 for baseline and endpoint visits, $50 for the MRI scan, and $15 for each of the 6 treatment intervention sessions. Compensation will be disbursed via Electronic Funds Transfer (EFT) using the veteran's preferred method (ex. Direct Deposit or Direct Express Debit card, etc.). Veterans who are unable to utilize this option may not be able to receive compensation. Participants will have an opportunity to discuss this option prior to consenting to participate in the study.

8.0 Alternatives to Participation

The alternative to participation in this study is not to participate. Participants may decide at any time to stop study participation and withdraw. There are no consequences for termination of study participation.

FUTURE USE OF DATA

As part of efforts to evaluate the study data for the development of future clinical studies, data collected during study participation may be made available upon request to researchers and scientists in accordance with federal guidelines and Hines local policy without additional consent from the participants. Identifiers will be removed from the identifiable private information and, after removal, the information could be used for future research studies or distributed to another investigator for future research studies.

Only authorized research personnel will have access to both identifiable and de-identified study data. Safety data and neurobehavioral data will be kept in your folder in a locked cabinet in a locked office.

9.0 Data Analysis

Data Collection and Analyses by Aim:
Aim 1: Develop a novel, combined iTBS+yoga intervention for Veterans with mTBI and chronic musculoskeletal pain. We will determine 2 main factors to finalize the combined iTBS+yoga treatment. First, our study team will conduct mock iTBS and yoga sessions to determine how many people we can feasibly provide iTBS to individually before starting the group yoga sessions in order to maximize the 60-min of enhanced MC plasticity induced by iTBS. We anticipate that we will be able to include 3-6 people per group. Second, based on our conceptual model (**Fig 1**), we will incorporate psychosocial education sessions that focus on pain beliefs, acceptance and catastrophizing into each of the 6-existing resilience-based psychoeducation sessions. We will engage key stakeholders in developing and finalizing these 20min. psychoeducation sessions, such as the Shirley Ryan Ability Lab's pain center, the Hines VA TBI/polytrauma and pain clinics, and the Veterans Engagement Panel.
Aim 2: Examine the feasibility and acceptability of iTBS+yoga Veterans with mTBI and chronic musculoskeletal pain. For feasibility, we will track the number of sessions completed and compute completion percentage rates as metrics of feasibility. If a participant misses a session, they will be contacted within 24 hours to determine reasons for missed sessions, which will also be tracked in an activity log. The participant will then be encouraged to make up their missed session. If participants miss less than 50% of the sessions (3/6) they will have the opportunity to make up the missing sessions. Thus, feasibility completion rates will be described according to reasons for participants not completing the 6-week intervention, and rates of missed sessions.

Regarding acceptability, the semi-structured interviews will be audio-recorded, transcribed verbatim and analyzed by 2 qualitative experts using thematic coding and constant comparison techniques. Qualitative analysis software will be used to support analyses. Our qualitative

analysis approach will be both deductive and inductive[29]. We will develop an initial code list a priori that reflects categories of interest, based on elements of our conceptual model. Within each category, we will inductively develop additional codes and analyze the text for themes and patterns. This will be an iterative process where our code list may be revised to account for novel instances in the data. We will continue until saturation[30] is reached across categories. Established qualitative analytic techniques will be used throughout this process, including the constant comparative method, which involves identifying key themes and concepts emergent from the data to generate meaningful categorization[30]. We will leverage a team-based approach drawing on the breadth of expertise of our team. Dr. Etingen and Ms. Billups will first independently review and open-code 2-3 transcripts to identify prominent themes. They will compare their codes, develop a set of analytic categories agreed upon through discussion, and develop the initial code list. They will continue with the next set of transcripts to develop new codes and revise codes applied to all prior transcripts, until they reach saturation with codes and themes, and finalize a codebook. They will then code un-coded transcripts until they reach inter-coder reliability greater than >0.90%[31].

Aim 3: Establish the foundation for sample size and power considerations for a future clinical trial to examine the effectiveness of iTBS+yoga on Veterans' QOL, function and pain outcomes.
Both sessions completed, and outcomes (QOL, function and pain) will be scrutinized for outliers and missing values. We will try to understand causes of missingness and input the missing values accordingly. We will perform normality tests for each outcome and transform data to obtain normal distributions. For each outcome, we will perform a paired t-test, between baseline and endpoint scores ($\alpha = .05$). To measure the pairwise association between two outcomes, we will compute Pearson correlations, and test for significance using the Fisher Z-transformation. We will also examine the relationship between number of completed sessions and change score (endpoint - baseline) of each outcome with a linear regression model. We hypothesize that the relationship will be positive, that is more sessions will provide better change scores. We will extract information from this pilot study and compute effect sizes based on change score for each outcome and compute sample size for 80% power with a 5% type 1 error rate. To determine the effects of iTBS+yoga relative to the LoveYourBrain Yoga program alone, we will also complete unpaired t-tests ($\alpha=.05$) on TBI-QOL and satisfaction ratings between data collected with this SPiRE and retrospective published data collected by Dr. Donnelly (consultant)[9-11].

Expected Outcomes: It is expected that Veterans with mTBI and chronic musculoskeletal pain will be able to attend the weekly sessions for six weeks. The quantitative satisfaction ratings will improve by the completion of the treatment. The semi-structured interviews and feedback will allow for modifications to be made as warranted. While we expect that the 3 outcome domains of QOL, function and pain all improve, even if a single domain improves, we consider this positive. By exploring the associations between the above outcomes, we will better be able to interpret which outcome domain may be driving improvements.

10.0 Confidentiality Plan

Loss of confidentiality is a potential risk. This research study involves collection of self-report questionnaires and assessments. All hard copies of questionnaires and assessments as well as urine screens and saliva alcohol test screens will include a unique participant identification number and the date the assessment was completed. Thus, it will be de-identified. The only identifiable information will be the participant's demographics questionnaire, contact information and EFT processing form (VA form 10-7078). The demographic questionnaire will be kept in a

locked filing cabinet in a locked office of the study PI, Dr. Herrold. The participant's name and contact information will be linked to the unique study identification number and saved electronically on a secure VA crosswalk server at Hines VAH. This secure crosswalk file is the only place where the participant's name will be linked with the unique participant identification number. The study PI, Dr. Herrold will have control over all research team members' access to the crosswalk file. The completed EFT processing form will be stored with the signed consent and HIPAA documents within a locked filing cabinet, in a locked office within the secure research area, to centralize documentation containing PHI/PII and minimize risk of an information breach.

Any breach in security will be reported to ACOS/Research, Facility Information Security Officer (ISO) and facility Privacy Officer within one hour. To protect from breach of confidentiality, each participant will be assigned a unique identification number by the study personnel and the only place where this participant identification number will be linked to identifying information (e.g., name, address, phone number, date of birth, social security number) will be on a cross-walk file within secure Hines VAH servers.

All urine samples or data will be marked only with the participant's identification number and date of collection in order to guard against privacy risk. Any hard copies of urine tests or data will not include any participant identifiers and will be kept in the participant's file in a lockable filing cabinet located in the PI's lockable office at Hines VAH. All urine tests or other data entered will be done in an electronic database on the Hines VAH secure data server. No information, including results from urine tests will be entered into the electronic medical record.

All data entry and analysis will be completed and saved on secure Hines VAH data servers. The Hines VAH data servers will be accessed at Hines VA Building 1, Room B351, B313, B317, and B321. The study PI, Dr. Amy Herrold, will access secure data servers remotely with an encrypted, VA-issued lap top computer. Data entry and data analysis will be completed on desktop computers located at Hines VAH, Building 1, Room B317, B321, and B313 or on Dr. Herold's VA-issued and encrypted lap top computer. No identifiable information will be saved on this laptop. However, de-identified information will be saved on the hard drive of this laptop and will be backed up by transferring data to the secured Hines VAH data server via an encrypted memory stick after data from each new subject has been collected. These laptops, therefore, do not contain the only copy of research information.

All information collected will remain within the VA. Until a schedule for local research records is published, all records including identifiers must be retained. Once a study team member leaves, his/her access to study data will be terminated.

The storage location for hard copies of all research related materials (e.g., consents, questionnaires, neuropsychological assessment forms) will be kept in a locked cabinet in the office of the study PI, Dr. Amy Herrold. Her office is located at Hines VAH in Building 1, Room B351, which is behind secured key-card access doors. All de-identified data and data analyses will be stored on a secured data server.

MRI data will be de-identified and uploaded to Hines VA secure server.

11.0 Monitoring and Reporting Serious Adverse Events

An adverse event (AE) is any undesirable experience associated with iTBS measured as a deleterious change from baseline on the Data Safety Monitoring Scale (DSMS). AEs can be non-serious and serious. A serious AE is when the changes are disabling, life threatening,

require hospitalization or requires intervention to prevent impairment. We will measure deleterious changes in (1) neurologic status including cognitive symptoms, (2) somatic and vestibular symptoms, (3) and depression. AE will be tracked using the AE log.

Amy Herrold will be responsible for training other research staff of the protocol set forth in this IRB application. All serious, unanticipated adverse events which are related to this research study will be reported to the IRB within 5 days. If any unanticipated problem occurs such as deviation to this protocol that involve risks or has the potential to recur, this information will be reported by the investigator to the IRB as well within 2 business days but no longer than 5 business days of the investigator or staff becoming aware of the event.

Finally, any finding of noncompliance, other deficiencies that substantively compromise the effectiveness of the facility's research information protection program, or suspensions or terminations will be reported to the ACOS/ACME/Research, Facility Information Security Officer (ISO) and facility Privacy Officer within 5 days of becoming aware. Any loss of confidentiality falls under immediate reporting requirements and will be reported within the hour of becoming aware.

This study will not have a Data Safety Monitoring Team.

12.0 References

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