Neuromodulatory Treatments for Pain Management in Veterans With Complex TBI Using Mobile Technology

NCT03418129

Document Date: December 5, 2022

Purpose of the Study

Aim 1: Examine the effectiveness of mobile interventions for reducing pain symptoms in Veterans with complex TBI. Hypothesis 1: Given preliminary data and empirical support for neurofeedback and mindfulness, we hypothesize that Veterans in the two intervention groups will report less pain at 3 months compared to Veterans in the control group.

Aim 2: Investigate the impact of neurofeedback and mindfulness on brainwave activity in Veterans with complex TBI and chronic pain. Hypothesis 2: Given research on electroencephalogram (EEG) and pain, we hypothesize that Veterans in the two intervention groups will show increased (8–12 Hz) alpha power at 3 months compared to Veterans in the control group.

Given connections to adverse outcomes, we will explore whether neuromodulatory interventions impact: (i) risk behaviors, with a hypothesis of lower levels of suicidality, aggressiveness/ violence toward others, and use of alcohol and drugs for the neurofeedback and mindfulness groups compared to the control group; and (ii) heart rate variability (HRV), with a hypothesis of significantly greater improvements in HRV compared Veterans to the control group.

Background & Significance

Traumatic brain injury (TBI) and chronic pain are common and serious health problems for Veterans of Operations Enduring Freedom, Iraqi Freedom, and New Dawn (OEF/OIF/OND) and often co-occur, leading to poor post-deployment adjustment. Pharmacological treatments for pain elevate risk of opioid abuse, and research suggests veterans perceive barriers to existing non-pharmacological, clinic-based treatments.

Thus, there is an urgent need to develop pain management approaches that are effective, overcome barriers to care, and are readily usable by Veterans. Evidence suggests that two neuromodulatory treatments, neurofeedback and mindfulness, reduce pain-related symptoms, are grounded in understanding of neurophysiological mechanisms of pain, and have the potential to be developed into self-implemented treatments through use of mobile technology. Preliminary data from our research team shows feasibility and benefit of mobile neurofeedback for pain management among Veterans with complex TBI, including data suggesting decreased emotional dysregulation and pain intensity immediately after using mobile neurofeedback. Similarly, studies show that mindfulness can be used outside the clinic and on mobile apps, but to our knowledge, no research has evaluated using mindfulness on mobile devices for pain management.

Design & Procedures

This study is a prospective, three-arm, randomized controlled trial of neuromodulatory treatments for chronic pain, enrolling 300 post-9/11 veterans with co-occuring pain and TBI. Participants will be scheduled for a baseline interview at Dr. Elbogen's research office at Duke or via WebEx/Zoom after

passing a preliminary telephone screen. All contact information for individuals who are identified as potential participants will be destroyed if they refuse or are ineligible to participate in the study, except for names. To avoid duplicate screens, we will keep a separate list of names only of all people who have been screened or refused to participate. No other sensitive information will be recorded in that document.

After providing informed consent, participants will complete an assessment including clinical interviews for TBI, chronic pain, and cognitive function; self-report instruments measuring chronic pain, TBI outcomes, suicidality, violence/aggression, drug and alcohol use, mental health, demographics, military experience, behavioral activation (BADS-SF) and medications/treatment, and an EEG/ECG reading. Participants will be assigned to one of three groups (n=100 in each): neurofeedback [using a (Muse) portable EEG headset and Mobile Muse: the brain sensing headband Neurofeedback app created by our group], mindfulness (using a mindfulness app created by our group, derived from the DoD and VA Mindfulness Coach app), or unstructured relaxation/control (using a relaxation app, also created in-house). All participants will receive an iPod Touch, be trained to use their respective app and instructed to practice 10 minutes a day, 4 times a week for 12 weeks, and be set up to receive reminders to practice from their iPod Touch or smartphone calendars. If participants prefer to receive reminders on their smartphone, they will be instructed to add a reminder in the calendar app on their smartphone that reminds them to complete their 10-minute practice sessions 4 times per week. Participants will be asked to report their current level of pain, stress, and anger before and after each session. Study coordinators will conduct two home visits (week 1 and week 6) and two phone calls (week 3 and week 9) to reinforce training, troubleshoot difficulties, observe participants utilizing the intervention in their home environment, and collect data on usability and tolerability. Follow-up data will be collected upon completion of the intervention at 12 weeks and again at 24 weeks. During both follow-up visits, veterans will complete clinical interview, pain assessment, self-report instruments including current traditional and alternative pain treatments, and EEG/ECG reading. Due to COVID-19, some participants will be asked to complete visits remotely. Coordinators will conduct "home visit" phone calls and will conduct baseline (screening/enrollment) follow-up interviews over the phone or via WebEx/Zoom, as needed. During these visits, there will be no EEG or HRV readings or cognitive testing. Data will be downloaded from the iPods once they are shipped back to our Duke offices following the participants' completion of the intervention at 3 months. For remote follow-up visits, participants will complete part of the visit over the phone and/or WebEx/Zoom, emailed a Qualtrics link to complete survey questionnaires, and emailed a FedEx label for shipping study equipment. Intervention Training will be combined with Home Visit 1 for remote visits, and we will follow up with a short phone call ~1 week later to assess for adverse events and safety measures. We will also ask two home visit questions, "Can you give any examples of specific times or situations in which the intervention was helpful?" and “What problems, if any, have you had using the app since you last talked with us?”

Selection of Subjects

Inclusion criteria:
-18 years of age or older
-Served in one of the military branches (Army, Navy, Marines, Air Force, or Coast Guard) in OEF

/OIF/OND (since October 2001)
-Meets DoD criteria for diagnosis of a TBI, defined as a traumatically induced structural injury or physiological disruption of brain function, as a result of an external force, that is indicated by new onset or worsening of at least one of the following clinical signs immediately following the event:

- Any alteration in mental status (e.g., confusion, disorientation, slowed thinking, etc.).
- Any loss of memory for events immediately before or after the injury.
- Any period of loss or a decreased level of consciousness, observed or self-reported.
- External forces may include any of the following events: the head being struck by an object,
- the brain undergoing an acceleration/deceleration movement without direct external trauma
- to the head, or forces generated from events such as a blast or explosion, including
- penetrating injuries.

-Reports chronic musculoskeletal and/or neuropathic pain, defined as moderate or severe pain (≥ 4 on a 0-10 rating scale) in one or more body regions for the previous 3 months or more.
-For individuals on pain medication, inclusion criteria are that (a) their pain medication regimen has been stable for the past 4 weeks, (b) they do not expect any major changes in their pain medication regimen for the duration of the study, and (c) they do not expect to have surgery or to be hospitalized for pain treatment for the duration of the study.

Exclusion criteria:

-History of epilepsy, seizure disorder, or any seizure or epileptic fit.
-Individuals with implanted medical devices that could experience interference during EEG and /or ECG, such as a spinal cord stimulator or pacemaker.
-Unable to provide informed consent.
-Note: For remote visits, participants must have access to the internet. Thus, any potential participant who is eligible but does not have internet access will be deferred until they can be seen in the office.
-Participants outside of the state of North Carolina will be permitted to participate in the study remotely since there are currently no in-person requirements for study visits.

Subject Recruitment and Compensation

Participants will be recruited using a multi-pronged approach, including distribution of IRB approved flyers and email scripts at the Durham VA Medical Center and through veteran organizations, community organizations, universities and colleges, medical and outpatient centers in North Carolina, and local businesses/community spaces, as well as through targeted Facebook ads and posts. Individuals interested in the study can self-identify by using the contact information to speak with a study coordinator. Participants may also follow a link to a REDCap survey (disseminated via social media ad/post, study flyer via a QR code, at recruitment events, and on the lab webpage), fill in their contact information, and request that a study coordinator contact them for a phone screen. Participants will also be recruited through research registries of individuals who have consented to be contacted about research studies including the Duke Behavioral Health and Technology Lab Data Repository (Pro00076336) and the Durham VA Mental Illness, Research Education, and Clinical Center (MIRECC).

We will also identify participants using the tools available in Maestro Care to help identify and recruit potential participants before consent is signed. Only key personnel who are delegated the task of patient identification/ recruitment will have access to report information in Maestro Care. Participants will receive a MyChart message, and study staff will contact them for a phone screen.
Participants who complete the study remotely will not be excluded based on geographic location since there is currently no requirement for in-person visits.

Up to 400 participants will be consented, for a total of 300 participants randomized to treatment arms. Participants will be compensated $100 for each in-office interview session, up to a total of $300. Participants traveling from outside the Triangle (≥30 miles) will be given the Duke rate per mile traveled for in-office interview sessions, up to a total of $100 per interview. For remote 3 month follow-up visits, in lieu of travel reimbursement, we will compensate participants $35 for returning their study equipment, to for the time and travel required to ship materials back to us. Participants will be allowed to keep the iPod Touch they used during the study after completion. Participants who do not complete the study will be asked to return the iPod.

Study Interventions

Neurofeedback: The proposed study intervention for the neurofeedback group involves two components, the Muse portable EEG headset and the 'Mobile Neurofeedback' app. Study participants engage in neurofeedback to practice meditation and induce relaxation, with the goal of reducing pain symptoms. Participants will be given a mobile neurofeedback headset, the Muse, which connects to the 'Mobile Neurofeedback' app via Bluetooth. During a 'Mobile Neurofeedback' session, individuals receive continuous neurofeedback, rewarding them whenever EEG signals move into patterns of brain activity that indicate a calm, relaxed state. Using 'Mobile Neurofeedback,' participants can select a soothing sound to help them gauge how relaxed they are and track neurofeedback progress. Participants will be instructed to use Muse + 'Mobile Neurofeedback' a total of 10 minutes a day, 4 times a week for 12 weeks.

Mindfulness Training: The study intervention for the mindfulness group uses a Mindfulness app created by our study team, derived from the "Mindfulness Coach" app, which was created by the Department of Defense's National Center for Telehealth and Technology in partnership with the Department of Veterans Affair's National Center for PTSD. The app was modified to function and appear aesthetically similar to the Mobile Neurofeedback app. This app enables individuals to practice the foundational features of mindfulness, which as described above, has been shown in other contexts to be effective for reducing stress, improving emotional balance, increasing self-awareness, helping with anxiety and depression, and coping more effectively with chronic pain. Using an iPod Touch received at their initial study visit, individuals will perform the app's Mindful Breathing and Body Scan exercises. The Mindful Breathing exercise guides users to focus their attention on their breath, to non-judgmentally notice when they become distracted, and to then direct their attention back to their breath. The Body Scan exercise guides participants to direct their attention to different parts of their body, noticing the sensations they feel without judging or trying to change them. These have both been adapted into 10-minute audio-guided exercises with stepby-step instructions. Participants will also have the opportunity to select a relaxing musical or

ambient background sound, identical to the choices in the Mobile Neurofeedback app, which will play in the background of the guided exercises. Participants will be instructed to complete these sessions 4 times a week for 12 weeks.

Unstructured Relaxation (control group): The control group will use a Relaxation app, which is designed to promote relaxation. The Relaxation app, also created by our study team, is aesthetically similar to the Mobile Neurofeedback app and offers the same relaxing background sounds with nature images. To create the most relaxing experience, users can choose a background sound and adjust the volume. Sessions are set for 10 minutes, and participants will be instructed to complete these sessions 4 times a week for 12 weeks.

All participants will be asked to report pain, anger, and stress symptoms before and after each session. All apps include their own logging systems to track usage. Research staff will also directly collect this weekly app usage data from participants' iPods a total of six times (at the two home visits, the two phone calls, and at the 3 and 6-month follow-up visits) during the study period. Devices will be labeled according to FDA requirements for non-significant risk devices. To preserve blinding to study condition, the same label will be used on all devices and will include the most significant side effects possible from any of the interventions.

Risk/Benefit Assessment

We believe that this study poses minimal risk to participants and that the risk-to-benefit ratio in the proposed study is acceptable. Anticipated risks related to neurofeedback include drowsiness after neurofeedback practice sessions and minor discomfort due practicing neurofeedback. There is also the chance that participants may experience headaches, dizziness, fatigue, tingling sensations, negative feelings such as anxiety or frustration, or increased risk of seizures among individuals with epilepsy or seizure disorder, although these side effects are rare. To minimize these risks, participants with a history of seizures will be excluded, and all participants will be instructed to practice neurofeedback at a time when they will not need to perform tasks that require high levels of alertness, such as driving or operating machinery. Participants are warned about each side effect prior to enrolling in the study and reminded again during neurofeedback training. Veterans will be asked if they have experienced any side effects during each scheduled study interaction and are instructed to contact research staff if they experience any of these adverse effects in conjunction with using the neurofeedback. Participants are instructed to discontinue use of neurofeedback if any of these adverse effects begins to affect their daily activities.

Mindfulness training or the control relaxation condition do not present a potential for serious risk to the health, safety, or welfare of a subject. It is possible that the process of learning mindful awareness may temporarily increase feelings of discomfort due to increased awareness. Veterans in the mindfulness and relaxing sounds groups will be instructed to discontinue the intervention if they experience any previously unknown adverse effects, to seek medical assistance if they require it, and to report the adverse effects to the researchers.

It is possible that some participants may become upset by interview questions, i.e., in response to

questions that ask about sensitive personal information or traumatic experiences. Participants will be made aware of what to expect during study procedures prior to their participation, and they will be informed in the consent form that the procedures may potentially lead to more distress. Participants will also be informed that they may discontinue their participation at any time. Interviews will be conducted by research staff trained in interviewing and de-escalation. Veterans who become upset during the interview will be informed that they need not complete the interview and that our staff can make arrangements for them to see a clinician at the mental health center. Finally, there is a risk of breach of confidentiality associated with any research. See section 14 below regarding steps to minimize the risk of breach of confidentiality.

This study advances the field by testing the efficacy of portable, technology-based neuromodulatory approaches by permitting Veterans to manage pain in a self-directed manner outside a clinic setting. This project will be the first to test the efficacy of such interventions in a population of Veterans reporting frequent and intense chronic pain, namely, post-9/11 Veterans with complex TBI. If we find that neurofeedback or mindfulness delivered via mobile technology is effective in reducing pain, our research team is uniquely skilled to examine whether the intervention also reduces maladaptive behaviors such as drug abuse, violence, and suicide. Both self-directedness and mobility address barriers Veterans report with traditional treatments. Developing alternative treatments would also reduce dependence on pharmacological treatments, reduce the need for clinic visits, minimize associated stigma, and allow patients to feel actively engaged in their own treatment. Participants may also benefit personally from being in this research study by experiencing reduced pain symptoms.

Data Analysis & Statistical Considerations

After accounting for a 3-month attrition rate of 10%, our targeted sample of 300 (100 in each treatment arm) will have 80% power to detect an effect size equivalent to Cohen's d = 0.42. This corresponds closely to findings from a published clinical trial of neurofeedback to reduce chronic pain (Jensen et al., 2013), which found 3-month improvements in pain intensity (0-10 rating scale) equivalent to Cohen's d = 0.38. Unless otherwise specified, we will fit a mixed longitudinal model with change from baseline to 3 months and 6 months as the response variable, pain stratification group as a blocking factor, randomized treatment as the between-subjects factor, month as a within-subjects factor, the interaction between treatment and month, and baseline score as a covariate. We hypothesize Veterans in the two intervention groups will report less pain at 3 months compared to Veterans in the control group. We also hypothesize Veterans in the two intervention groups will show increased (8–12 Hz) alpha power on EEG at 3 months compared to Veterans in the control group.

Data & Safety Monitoring

Participants will be screened and excluded from study participation if they have epilepsy/seizure disorder. Potential participants will be asked about seizures twice prior to enrollment in the study intervention: once on the phone screen and again during the initial study interview. Participants will be told to discontinue the study intervention if they develop a seizure disorder or have a seizure. Participants will also be asked about seizures at weeks 1, 3, 6, 9, and 12 of study participation, and will be told to stop the intervention if they report one.

During study participation, participants will be asked about and monitored for all adverse reactions. Individual participants will be told to discontinue their use of the study intervention if they report a moderate or severe adverse determined to be possibly or very likely related to the study. These participants will be instructed to no longer practice the intervention for the duration of their participation, but will be given the opportunity to complete the rest of study data collection visits. Participants will also be routinely asked about suicidal ideation and violent ideation. Participants who report suicidal or homicidal ideation with a plan will be instructed to discontinue their use of the study intervention. We will be reporting every 6 months to an external Data Safety and Monitoring Board (DSMB) independent of the sponsor. The DSMB will monitor subject accrual (including participant withdrawal) and adverse events. They will also provide consultation on safety issues as needed throughout the study.

When a participant expresses suicidal or homicidal ideation, study staff will respond using a standard of practice that has been used successfully in other studies involving military veterans at Duke University (See “Duke specific Psychiatric Emergency SOP” document for the process, and the “Risk Screen Documentation” document for questions used for suicidal and homicidal ideation assessment). The study staff member responsible for the interaction with the participant will be instructed to gather more information from the participant, including information about suicidal plan, means, intent, and history of suicidal behavior. Based on participant’s responses and risk, study staff may respond in a number of ways including offering resources, asking about participant’s linkage to treatment, recommending further evaluation at the ER, initiating involuntary evaluation, or other responses deemed clinically appropriate. If the participant reports ideation over the phone, the participant will be informed that the PI may contact him/her to talk more about his/her thoughts. The study coordinator will obtain current contact information for the participant and inform the PI, who will contact the participant as necessary to ensure participant safety.