Neurofeedback-enhanced mindfulness meditation for the treatment of affective and attentional disturbances in traumatic brain injury patients

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Background and Significance

Historical Background:

Mindfulness meditation (MM) involves the non-judgmental paying attention to moment-to-moment experience. In contemporary, Western society, the practice is now widely used to improve psychological well-being, treat anxiety and mood disturbances, decrease stress and train attention, among other uses. A substantial and ever-growing scientific evidence base supports many of these efforts. Numerous studies demonstrate MM's capacity for the attenuation of psychological distress (Keng et al. 2011). Meta-analyses have demonstrated how the practices can significantly impact symptoms of anxiety and depression (Hofmann et al. 2011). A handful of studies have also evaluated the impact of MM on various facets of attention, though results have been less consistently favorable (Chiesa 2011).

Given its ability to improve stress and mood and possibility inattention, MM appears especially well suited to treat persistent symptoms of mild traumatic brain injury (mTBI). Every year in the United States, more than 1.4 million people suffer from TBI, 75% of which are considered mild (CDC). While the majority of patients with mTBI make a full recovery within the first year after head injury, a substantial percentage of patients, estimated between 5% (Iverson 2005) to 15% (Alves 1993), go on to have persistent physical and psychological symptoms, such as headache, dizziness/vertigo, impaired balance, memory deficits, inattention, slowed processing, hypersomnolence, fatigue, insomnia, depression, anxiety, and irritability (Glenn and Herman 2007). A growing body of literature has begun exploring the utility of MM in the treatment of mTBI symptoms, with positive results now accumulating for its impact on quality of life and depressive symptoms (Bedard et al. 2005), and possibly attention (Azulay et al. 2013; McHugh and Wood 2013).

Meditation can prove challenging, however, especially for the neurologically injured who suffer from persistent inattention and distractibility. A recently launched consumer product, "MUSE: the brain-sensing headband" aims to facilitate medication practice, cueing users into the success of their technique and helping them stay motivated to sustain a consistent practice (www.choosemuse.com). MUSE is a neurofeedback (NF) device that uses frontotemporal scalp electrodes to measure synchronous, postsynaptic potentials in the cortex represented as oscillatory EEG waves. These waves are mathematically transformed into an auditory neurofeedback signal that is fed back to users, training them to maximize relaxed, attentive and minimize distracted states of mind. Neurofeedback generally works through operant conditioning, enabling individuals to learn to control and/or change their brain activity over extended practice. User's performance and progress is tracked over time on a mobile device. By providing users with real-time feedback and gamifying their practice, MUSE aims to make meditation a more appealing and sustainable practice. These features may be of special relevance for the mTBI population.

In our study, we wish to evaluate the efficacy of a simple MM intervention in chronic TBI patients, evaluating its potential impact on anxiety, depression, and attention. Our study will involve two groups of patients, those who practice regular MM and those whose MM is enhanced by NF. We hypothesize that MM both with and without NF-assistance will lead to improvements in anxiety and depression scales. We further hypothesize that by optimizing a MM practice, MM-NF will lead to improvements in attention, as well as improved receptivity of the practice overall.

Previous clinical studies of MM on anxiety and mood:

In the last several decades, numerous studies have established the efficacy of MM in the treatment of mood disorders. A recent meta-analysis concluded that mindfulness-based therapies can reduce symptoms of anxiety and depression, with large effect size in patients with anxiety and depressive disorders and moderate effect size in the more general population (Hofmann 2010). The benefits of MM on anxiety and mood would likely extend to symptoms

within the mTBI population as well. Mood disturbances following TBI is very common, with cumulative rates of depression estimated at 61% and anxiety at 70% (Hibbard et al. 1998).

A handful of studies have evaluated the impact of MM on mood disturbances in TBI. A pilot study employing a group mindfulness-based intervention in a TBI population showed improvements in quality of life after 12 weeks (Bedard et al. 2003). Improvements were maintained at follow-up one year later (Bedard et al. 2005), however no control patients were included in this latter study, making passage of time and/or placebo effects a possible explanation for the findings.

Attention in TBI—cognitive training and mindfulness-based training:
Attention training for the chronic TBI population is a domain of cognitive rehabilitation that has received a lot of consideration in recent years. Several large reviews and meta-analyses (Cicirone 2011; Ponsford 2014) similarly conclude that chronic, post-TBI attentional deficits can be at least partially rehabilitated through repetitive, task-based training.

Within the TBI literature, the modality with the most robust and promising literature is a cognitive strategy, Attention-Process Training (APT), a computer training game designed for patients with acquired brain injury that aims to rehab multiple subcomponents of attention. The concern with APT is despite improved performance on program tasks, training may not transfer to novel cognitive tests (Zickefoose, et al. 2013). Two small studies, however, have shown that improvements on APT do transfer to novel attentional tasks as measured by standard neuropsychological tests (Palmese et al. 2000; Pero et al. 2006). A more rigorous study of APT is currently being undertaken (Bartfai et al. 2014).

A growing body of evidence has examined the role of mindfulness meditation as a method of attention training in adults. Contemporary definitions of meditation define the practice as "attentional regulatory training" (Lutz et al. 2008). Studies have shown improvements following MM in executive attention (Tang et al. 2007; Wenk-Sormaz 2005; Ainsworth 2013) and attentional discrimination (Semple et al. 2010). Such studies compare pre- versus post-MM outcomes on objective neuropsychological tests—suggesting that MM does in fact transfer to novel tasks. On the contrary, a substantial number of studies have also failed to show MM to be beneficial to attention training (Anderson et al. 2007; MacCoon et al. 2014).

A smaller subset of studies have evaluated the impact of meditation on attention among TBI patients. Cognitive benefits of MM in a TBI population have been demonstrated on an over-selectivity task (McHugh and Wood 2013) and executive aspects of attention (Azulay et al. 2013). In a more rigorously designed RCT, however, MM practice in a TBI group was not associated with improvements on attention tasks (McMillan et al. 2002). According to the major cognitive rehabilitation reviews for TBI, the literature on MM for attentional training is not robust enough to recommend outside of a research protocol at this time (Ponsford et al. 2014). We feel that by using NF to assist a practice of MM, MM would be more likely to significantly improve attention.

Neurofeedback:
NF has been studied as a treatment numerous neurological and psychological disorders including anxiety and depression (Hammond et al. 2005), and ADHD (Vollebregt et al. 2014). Research shows that when participants are shown their brain waves in real-time, they are able to alter their frequency. Whether or not this translates to meaningful clinical impact is a matter of debate. A review on NF for the chronic TBI population cited multiple studies demonstrating the utility of using NF for the treatment of attention, impulse control, executive functioning, and processing speed, however the authors remarked that most studies included in this review lacked rigor (May et al. 2013). In fact, some strongly argue that in general, the benefit of NF as more generally applied to all clinical populations represents non-specific effects related to

placebo effects and expectancy (Thibault et al. 2015). Currently, the FDA has only approved NF devices as a relaxation tool.

NF and MM have many similarities—both can be used to train relaxed, focused mental states, improve attention, and build emotional control—and differences—MM being "self-regulated" and NF "machine-aided" (Brandmeyer and Delorme 2013). The use of NF as a tool to enhance MM by detecting mind-wandering right as it occurs, is a novel concept.

Rationale behind the proposed research and potential benefits to patients and/or society: MM represents a safe strategy for treating mood and anxiety disorders and potentially aspects of attentional performance in a mTBI population. However due to this population's post-traumatic cognitive impairments, MM is a less accessible therapeutic strategy than it otherwise would be. MUSE, through its provision of NF and gamification, has the potential to help TBI patients initiate, sustain, and maintain a meditation practice. If MUSE outperforms MM on affective or cognitive outcome measurements, this study could function as a pilot study, informing future investigations of the product. If MUSE ultimately holds up in more rigourous studies, it should be recommended as a therapeutic tool to mTBI patients. If on the other hand, MUSE does not show any benefits over a regular practice of MM, the device would not be considered cost-effective and should therefore not be recommended to mTBI patients.

Specific Aims:
Aim 1: *Evaluate within group differences, whether a daily, six-week practice of NF-MM or MM or a no-treatment control leads to pre- versus post-treatment changes in affective, cognitive, or mindfulness-associated variables*.

Aim 2: *Evaluate across-group differences, whether NF-MM outperforms MM in affective, cognitive, or mindfulness-associated variables*, *or whether NF-MM or MM differ from a no-treatment control group.*

Aim 3: *Evaluate the change in mindful attention (as measured by EEG) between NF-MM and MM groups and the no-treatment control group at the end of the intervention.*

Aim 4: *Evaluate the relationship between the degree of mindful attention (as measure by EEG) and affective and cognitive variables across NF-MM/MM groups as well as the no-treatment control group.*

Aim 5: *Evaluate acceptability of and attitudes toward NF-MM in TBI patients*.

Subject Selection
Inclusion criteria: 1) history of mild-moderate TBI (per ACRM guidelines), 2) significant complaint of impaired attention or concentration, 3) ages 18-65, 4) >1 year since TBI, 5) significant cognitive function to participate in neurofeedback and mindfulness meditation, 6) has daily access to a smart phone, 7) no significant medication changes planned for the duration of the study, 8) has not had a significant meditation practice in the past.

Exclusion criteria: 1) severe mental illness or psychological symptoms (severe depression, suicidality, disabling anxiety, PTSD, psychosis, dissociation), 2) significant pre-morbid learning disability, 3) current or recent (in past year) history of significant drug or alcohol abuse, 4) medical illness severe enough to result in an attentional disorder, 5) neurodegenerative disease, 6) non-fluency in English.

Source of subjects/patients: Subjects will be recruited from a variety of settings including outpatient clinics and related clinical research projects of various clinicians including MDs,

SLPs, psychologists, and LCSWs at SRH and MGH, local TBI support groups, including BABIS (Boston Acquired Brain Injury Support Group), or the general population.

Recruitment methods: Recruitment methods will include word of mouth and dear colleague letters, email, list servs postings, flyers, as well as online posting on the partners RSVP for Health, Process Notes from MGH Psychiatry, Spaulding Weekly Spotlight publication, MA psych association listserv, and various social media outlets including LinkedIn and Facebook. The actual documents disseminated through these various above listed avenues will include all approved study documents which include approved poster with graphics, approved poster text (without graphics if dissemination avenue does not allow graphics—i.e. with a list serv), approved bullet-pointed list of study highlights, approved dear colleagues text.

Subject Enrollment

Methods of Enrollment: Interested participants will be instructed to call or email study staff who will give the patients a brief overview of the study, then perform a telephone or an online pre-screening.

Procedures for obtaining informed consent: Consent will initially be discussed with participants over the phone. On their initial pre-treatment visit, written consent will be obtained with either a study physician or psychologist.

Treatment assignment and randomization, if applicable: Patients meeting study criteria will be randomized into one of two groups, either the NF-MM or MM group on a rolling admission. Preliminary assessment after 10 subjects enrolled in the study, demonstrated that participants in the intervention (MUSE) group had higher rates of depressive symptoms than participants in the control group. In order to balance these groups, we subsequently have decided to stratify by depression scores, such that the next five enrolled participants would be placed in the MUSE group if they had lower than average (for the study) BDI scores or the control group if they had higher than average (for the study) BDI scores. After these five subjects were enrolled, we will recalculate average BDI scores and decide whether to continue to stratify by depression scores or not.

Additionally, we have decided to add a no-treatment control group of 10 subjects. These individuals will be recruited after the first 20 subjects complete the trial. Thus, 30 subjects in total will now be part of this study.

Study Procedures

Study Site: Pre- and post-treatment assessments will be performed in outpatient offices at SRH in Charlestown or Cambridge (for those enrolled in the SRH study). MUSE training session will occur during the pre-treatment assessment session for the intervention groups. This training will last approximately 30 minutes and include a MM session with or without auditory NF. Participants will then perform their 6 weeks of NF-MM with MUSE or MM without MUSE at their homes. Study staff will also call participants on a weekly basis, to remind patients to practice and provide technical support. A post-treatment assessment session will take place within one week of completion of the intervention. Those in the no-treatment control group, will simply undergo pre- and post-neuropsychological testing 6 weeks apart and receive meditation and MUSE training at their final 6-week visit.

Device to be used: MUSE hardware and Calm app software. MUSE is a consumer product, a "brain-sensing headband" lined with 7 frontotemporal EEG sensors that detect alpha, beta, delta, gamma, and theta waves. MUSE training begins with a calibration task whereby participants' EEG waves are compared between an attentional and relaxation task. The Calm app guides participants through a mindfulness meditation exercise, providing instructions for users to close their eyes, relax their body, and pay careful attention to their breath. During this meditative practice, EEG signals are fed back to patients through auditory feedback, a calm

versus noisy wind. When participants are consistently in a relaxed state, they will hear birds chirping. Through this auditory feedback, patients are trained to maximize their relaxed, attentive states, and minimize their distracted, tense states. User's performance and progress is tracked over time on a mobile device. MM controls will use a custom version of the Calm software for directed meditation without the MUSE EEG NF component. For further details regarding details of the MUSE device, please see attached documents.

Data to be collected:

1) Outcome measurements:
   a. Cognitive assessments: Trail-Making Test (from D-KEFS), Symbol-Digit Coding, WAIS-IV Digit Span (forward, backward, sequencing), the Connor's Continuous Performance Test 3rd version (CPT-3), and the Self Efficacy (SEsx) scale.
   b. Affective assessments: 1) Beck Anxiety Inventory (BAI), 2) Beck Depression Inventory (BDI-II), 3) Neurobehavioral Symptom Inventory (NSI)
   c. Mindfulness assessment: Cognitive and Affective Mindfulness Scale – Revised (CAMS-R)
2) Compliance to intervention: The Calm app will track daily meditation practice adherence in both the NF-MM and the MM groups.
3) EEG data for NF-MM or MM groups: The Calm app will track the percentage of time participants in the NF-MM group spend in a relaxed attentive state during training. Additionally at the end of the 6-week intervention, both NF-MM and MM groups will be asked to meditate while connected to EEG leads without auditory neurofeedback. The percentage of time spent in a calm, neural, and active state will be assessed here as well.
4) Qualitative assessment: Both NF-MM and MM groups will undergo a very brief qualitative interview at their post-treatment session to inquire on their subjective experience with MM with or without NF. The MM will then receive a MUSE device and practice NF-MM for two additional weeks, after which point they will receive a phone call with further questioning regarding their experience with MM with or without NF.

Biostatistical Analysis

First, we will power this study using the effect size that we calculate from the cognitive MUSE data collected by Bhayee et al. Then, we will compare our NF-MM, MM, and no-treatment control groups. We will contrast the three groups' cognitive outcomes in trail-making, symbol-digit coding, WAIS-IV digit spans. We will then compare affective outcomes using the Beck Anxiety Inventory, Beck Depression Inventory and Neurobehavioral Symptom Inventory. Finally we will compare mindfulness data from the Cognitive and Affective Mindfulness Scale. The continuous variables from the cognitive and affective measures will be analyzed with linear regression. The statistical contribution of demographic variables will be assessed using mixed effects models. We plan to perform post-hoc analysis for multiple comparisons.

Risks and Discomforts

Complications of procedures: We do not anticipate significant adverse effects from the use of MUSE technology, as it is already in wide use in the general population without reports of any significant harm. However, other neurofeedback studies have documented patient complaints of fatigue, feeling "spacey," anxiety, irritability, headache, or difficulty falling asleep (Hammond et al. 2011). Subjects will be able to contact study staff during daytime hours with questions or concerns regarding the possibility of such adverse effects. If these symptoms are believed to be stemming directly from use of MUSE and are intolerable for patients, they will be instructed to discontinue participation in the study.

Device complications/malfunctions: While it is not expected, it is possible for the MUSE device to malfunction. Participants will be able to email or call with tech support questions during standard business hours. Study staff members will call patients back to troubleshoot. While

equipment malfunction could interfere with data collection, it will not put patients at any risk of harm.

Psychological non medical risk: Meditation practice has very infrequent adverse effects. However in patients with severe mental illness (severe depression, suicidality, disabling anxiety, tendency toward dissociation), spending time silent, alone with one's thought in a repetitive practice can rarely exacerbate psychopathology. These patients will be carefully screened and excluded from participating in the study. If MM is stirring up unpleasant thoughts and feelings, they will be able to reach study staff members during business hours, and if necessary will be discontinued from the study. Participants in this study will also be asked to fill out the BDI-II form during pre- and post-test visits. A contingency plan is in place if participants exhibit suicidal ideation. Please see the attached document.

Disclosure of Confidential Information: All patient information will be kept confidential in this study and will not be shared outside of study collaborators. Subjects' data that is collected via MUSE will also be safeguarded. Please see the attached data handling form from MUSE. Importantly, subjects data that is stored on MUSE does not include personal health information. It includes the participant's username, email, frequency of MM training, and EEG waves during meditation. Users' accounts are also password protected.

Minimization of Risks: Risks of loss of privacy will remain as with any study. For this reason, all data collected from participants will be kept in a secure, password protected database. Trackable correspondence with participants, ie email, will be conducted through a secure exchanger. Participants' data will be de-identified at the onset of the study and assigned a subject number that will be used to keep track of their study data. A key linking patient's names and their study number will only be available to key research personnel. All study data will be stored in a secure location, maintained either electronically on a password protected computer or if on paper, in a locked cabinet in a private office or office requiring a security badge to enter. Printed computer data that is no longer needed for research purposes will be properly disposed of in secure, confidential medical paperwork waste bins.

Potential Benefits

Potential benefits to participants: Based on the mindfulness meditation literature, participation in the NF-MM or MM arms of this study is likely to have a positive impact on a patient's mood, anxiety, and biological stress levels. It may also help with attentional impairment. Individuals in the no-treatment control group will continue with care as usual. They are not expected to benefit directly from participation in this study.

All participants in all groups will receive a Muse device in compensation for completing the study.

Potential benefits to society (e.g., increased understanding of disease processes): Information from this study could potentially be useful to mTBI patients on a population level. If NF-MM is shown to significantly outperform standard MM in terms of psychological and cognitive performance, mTBI patients and their clinicians may want to consider using MUSE following brain injury. If NF does not enhance participants' practice of MM, mTBI patients and their clinicians will want to recommend against the use of the device, as its cost does not bear out in improved outcomes. If the NF-MM or MM groups outperform the no-treatment control group, results will suggest that various types of meditation interventions may be useful for affective or cognitive symptoms in individuals with traumatic brain injury.

Monitoring and QA

Independent monitoring of source data: Study staff, physicians or psychologists, will be responsible for reviewing the accuracy and completeness of form entries, case documents, and informed consent.

Safety and outcomes monitoring: Safety and efficacy data will be reviewed on a weekly basis through email or phone correspondence between participants and either a physician or psychologist study staff member. If the practice of meditation or use of neurofeedback is causing significant psychological distress or physical discomfort, the patient will be advised to discontinue participation.

Adverse event reporting guidelines: All reports of adverse psychological and physical effects will be relayed directly to the study PI and to MUSE.

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Study Schematic: see attached

Appendices

FDA approved drug: Not applicable; see attached user's manual for MUSE device

Schematic of Device (for device studies): please see user's manual for MUSE device

Patient/Ss recruitment material (advertisements, Dear Colleague letters, flyers, etc.): see attached

Survey tools if applicable: see attached