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OFFICIAL STUDY TITLE:

Feasibility and acceptability of stress induction, physiological data collection, and Mindfulness-Based
Stress Reduction among combat veterans with PTSD

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ORGANIZATION:

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1) Protocol Title

Feasibility and acceptability of stress induction, physiological data collection, and Mindfulness-Based Stress Reduction among combat veterans with PTSD

2) Objectives

Objectives are to gather feasibility and acceptability of key study elements (e.g., stress induction via cognitive stressor, physiological data collection including respiration, blood pressure, and heart rate, and the target intervention Mindfulness-Based Stress Reduction) among combat veterans experiencing PTSD symptoms to support a future K23 grant resubmission. Specific Aims are as follows:

Aim 1: Assess feasibility and participant acceptability of intervention and randomization procedures.
Aim 1A: Examine acceptability of MBSR via qualitative data gathered during a post-intervention focus group.

Aim 1B: Assess feasibility of recruiting and acceptability of randomizing participants to an MBSR or active control condition. Recruitment, differential retention, and home practice completion rates will be examined.

Aim 2: Assess feasibility and participant acceptability of concurrent stress induction and physiological data collection (i.e., systolic [SBP] and diastolic [DBP] blood pressure) procedures.
Aim 2A: Evaluate feasibility of stress induction via significant change in BP from baseline to stressor.
Aim 2B: Examine acceptability of physiological data collection concurrent with stressor task via focus group.

Aim 3: Evaluate sensitivity and responsiveness to change of outcome measures. Examining these qualities and pre-post changes in physiological and psychological resilience and PTSD symptoms will provide crucial information regarding relationships between the intervention and changes in relevant variables.

3) Background

Posttraumatic stress disorder (PTSD) is a significant public health concern[1] that negatively impacts quality of life and functioning,[1-3] is associated with increased mortality,[4] and poses an economic burden.[5]

Despite a need for effective interventions, front-line treatments are limited.[6-8] VA/DOD Clinical Practice Guidelines[9] recommend cognitive processing therapy (CPT) and prolonged exposure (PE). Although research supports these treatments,[10-12] they present significant shortcomings: (1) they may not be acceptable for all patients,[13] (2) they show attrition as high as 40%,[14-16] and (3) they often result in residual symptoms.[7,8] Symptoms such as higher physiological arousal[17,18] and stress reactivity[17-19] are related to dropout. Despite this relationship, status quo treatment approaches do not account for physiological factors related to PTSD.[20,21] Due to these limitations, alternative interventions and treatment targets for PTSD are warranted.

Mindfulness-Based Stress Reduction (MBSR) is a promising alternative.[1,22,23] MBSR is a mindfulness-based intervention (MBI) and shows promise for treating PTSD in veterans.[20,22,24-26] MBSR improves PTSD symptoms and benefits physiological systems related to PTSD symptoms[20] such as the autonomic

nervous system.[27] Despite promising findings, mechanisms by which MBSR may benefit PTSD are less understood.[28,29]

Increased resilience may be the primary mechanism in MBSR for PTSD. Resilience is *the ability to cope with, adapt to, or overcome exposure to stress*.[30] Psychological resilience is conceptualized as a trait[31-33] or a teachable skill.[34-37] Psychological resilience is negatively associated with the likelihood of PTSD.[38-40] MBIs may reduce avoidance of trauma-related stressors, thereby increasing psychological resilience and reducing PTSD symptoms.[41] MBIs effectively increase psychological resilience high-stress groups,[42,43] and increased psychological resilience mediates improvements in stress disorders.[44]

Physiological resilience is another promising mechanism, and is defined as the capacity of a biological system to avoid shifting away from baseline (e.g., "reactivity") or to return to baseline (e.g., "recovery").[45] The sympathetic nervous system (SNS) has served as an indicator of physiological resilience among veterans.[46-48] Specifically, physiological resilience is indicated by the magnitude of peripheral vasoconstriction,[48] directly related to blood pressure (BP).[49] BP has been conceptualized as an indicator of physiological resilience to negative health outcomes.[50] Combat veterans with PTSD exhibit low physiological resilience via exaggerated BP reactivity to acute stress.[51,52] Other research has found that trauma is predictive of lower physiological resilience.[53] MBSR[54-58] and resilience-based[59] interventions reduce BP, improve physiological resilience,[60,61] including among military personnel.[62] Prior to conducting a fully-powered mechanistic RCT, central research methods such as intervention, stress induction, and physiological data collection must be validated.

Feasibility and acceptability must be established. Although some studies have conducted RCTs of MBSR among veterans with PTSD,[23] feasibility and acceptability limitations remain. A systematic review currently under review by the PI found that MBIs for PTSD showed an average attrition rate of 21.3%; much higher than the general population.[63] The reason for this difference is unknown. A recent meta-analysis called for increased efforts to improve the feasibility and acceptability of MBIs.[63] Similarly, a recent review reported that data regarding adherence in MBSR (e.g. at-home meditation practice) is underreported in most studies.[64] No studies have evaluated the feasibility and acceptability of these facets of MBSR among veterans with PTSD. Further, no study has evaluated the feasibility and acceptability of a stressor task and concurrent physiological data collection in veterans. These aspects of feasibility require further study, as recent research has emphasized the need for stress induction tasks that are feasible and reproducible.[65] Given the novelty of these procedures in this population, and the potential impact of the PI's line of research among veterans underserved by status quo interventions, this KL2 application essential. To support this line of research, this KL2 will inform the resubmission of the PI's K23 proposal and forthcoming VA CDA.

The long-term goal of this research is to use mechanisms identified via a fully-powered mechanistic RCT funded by NIH K23 or VA CDA to optimize a resilience-based, trauma-informed MBI. In order to secure funding and conduct this mechanistic RCT, feasibility and acceptability of the stressor paradigm and concurrent physiological data collection, as well as the MBSR and randomization procedures must be established.

4) Study Design

The design of this study is a randomized controlled interventional study. All participants will complete three in-person lab visits, consisting of computerized questionnaires, physiological data recording, and completion of a stressor paradigm. Following completion of computerized questionnaires at the baseline visit, participants will be randomized at a 1:1 ratio using covariate adaptive randomization.

Participants will be randomized to receive Mindfulness-Based Stress Reduction (MBSR; active intervention condition) or Health and Wellness Education (HWE; control condition). Both interventions include 8 weekly in-person group sessions with an additional extended session after week 8.

5) Study Population

a) Number of Subjects

This is a single center study. We will screen approximately 40 patients of which we expect to enroll 20 participants, all of whom will be veterans experiencing PTSD symptoms (PTSD symptoms will be confirmed during telephone screen). Therefore, 20 participants will sign the consent form and be included in this study.

b) Inclusion and Exclusion Criteria

Participants will be screened over phone to determine eligibility. Subjects will be aged 18-85 years. Subjects older than 85 years of age will be excluded due to their decreased ability to tolerate the experimental procedures because of potential cognitive decline and inability to sustain the attention needed for the Portland Arithmetic Stress Task (PAST), as well as the decreased ability to remain still during the intervention conditions due to musculoskeletal aches and pains and decreased flexibility frequently seen in aging.

Inclusion criteria	Exclusion criteria
Adult (18-85 years)	Pregnancy
Military veteran	Severe untreated depression, cognitive impairment, or active suicidality*
Experiencing PTSD symptoms	Life-threatening or severely disabling medical conditions
Reading and speaking in English	Excessive use of alcohol, nicotine, or cannabis†
Be able to travel to OHSU for three two-hour lab visits, 8 weekly intervention sessions and one long extended session, and a two- hour focus group	

* Severe cognitive impairment will be determined by a score ≤ 20 on the Telephone Interview for Cognitive Status; active suicidality will be determined by endorsement of item 9 on the Patient Health Questionnaire.

† Alcohol use will be determined by a score ≥ 8 on the Alcohol Use Disorders Identification Test (AUDIT-C); excessive cannabis use will be determined by a score ≥ 7 on the Cannabis Abuse Screening Tool; excessive nicotine use will be determined by a score ≥8 on the Fagerstrom Nicotine Dependence Scale.

If a participant does not consent, or is excluded for any other reason (e.g. screen-failed), data already collected (e.g., demographic; screening data) will be retained for the purpose of characterizing individuals who made contact, as well as collecting and presenting feasibility and acceptability data to the VEG at the conclusion of this study. The reason for not enrolling will be noted.

c) Vulnerable Populations

No vulnerable populations will be recruited as part of this study.

d) Setting

This is a single site study. All research activities, including interventions, will take place at OHSU with the exception of some recruitment procedures that will take place at the Portland VA (e.g., presenting study materials to clinics).

e) Recruitment Methods

A multi-dimensional recruitment strategy will be used to achieve target enrollment numbers. We will use OHSU approved recruitment tools such as Epic Reporting Workbench, Slicer Dicer, Research Data Warehouse (RDW), etc., to query OHSU electronic medical records. This study will use Epic MyChart® to recruit potential participants. Researchers will use OHSU approved search tools as mentioned above to identify potential study participants. Potential participants will be sent a MyChart® recruitment message asking them to participate. There is no risk of duplicate invitations as it is based on MyChart® accounts combined with Epic records and no duplication is possible.

Social media advertising and community outreach and snowball methods (e.g. word of mouth) will also be utilized as avenues for participant recruitment. With the approval of OHSU clinical providers and the OHSU IRB (with the support of the mentorship team), additional outreach will take place at OHSU using clinic lists of patients who have opted into research opportunities. Only passive recruitment will occur at the VAPORHCS. Specifically, VA clinic staff may provide approved flyer with OHSU study contact to any interested Veteran who in turn may reach out to the PI or study team with questions if interested. A potential participant may then call the study team at the number on the flyer to schedule a phone call to be screened for eligibility. Dr. Kaplan may also provide OHSU IRB approved flyer (including study contact information) to VAPORHCS clinicians not affiliated to the study team to provide to any veterans who elect not to initiate, or who discontinue traditional PTSD treatments (e.g., Cognitive Processing Therapy (CPT) or Prolonged Exposure (PE) prior to completion. In addition to these recruitment efforts through VAPORHCS and OHSU, flyers will be posted via online outlets such as Facebook and Craigslist, and recruitment materials will be distributed to veterans with the Multnomah County Veterans' Services. OHSU also hosts online search engines that allows potential participants to filter research participation opportunities based on certain criteria (e.g., compensation, time commitment). Dr. Kaplan will also present information about this study to veteran community resources, including Veterans of Foreign Wars (VFW) groups. Finally, Dr. Kaplan will engage in quarterly meetings with the Veterans Engagement Group (VEG) through VAPORHCS.

Veterans Engagement Group (VEG). The VEG is a 7-10 member group comprised entirely of veterans who are VAPORHCS patients, former employees, and clinicians. This group provides investigators with feedback throughout the research process. The VEG regularly assists researchers in maximizing their recruitment and retention efforts, as well as providing feedback on aspects such as qualitative data collection and analysis as presented in this proposal. Dr. Kaplan has been invited to attend regular VEG meetings in order to ensure the effectiveness of recruitment methods, and to discuss alternative strategies in the event of slow recruitment. VEG will not have access to any patient data or identifier. Dr. Kaplan may present aggregate recruitment/enrollment data to VEG in case there are problems and seek their advice to improve enrollment.

Interested veterans will contact the research team to be screened for eligibility and to be informed of the purpose and procedure of the study. They may reach out by seeing the online flyers on social media platforms or hearing about the study during clinic visits or being handed a flyer. As a secondary strategy, upon identification of Veterans through OHSU approved recruitment tools, we will send a letter via US postal service or an email to explain the study. A study team member's name and contact information will be provided in the letter so that the potential participant can call in to express interest or learn more about the study. Participants will also have the option to opt-out by calling or emailing the study team if

they wished not to be contacted. But if no response from the potential participant, the study team will call the Veterans who were sent the letters to discuss this study opportunity.

Participants will be screened for eligibility by phone using a standardized list of inclusionary and exclusionary questions (Initial phone contact). The study and the participants' right in research and compensation plan will be explained. Those who are eligible will be invited to a second phone screening which will be scheduled according to a time convenient to the participant. During the second screening visit, eligible participants will be asked some questions related to demographics and will be required to complete some survey questionnaires to gauge their quality of life, cognitive status, etc. (see table below). If the participant qualifies screening, someone from the team will contact the participant and inform them of their eligibility and next steps. Participant's name and contact information (phone number, mailing address, email address), age will be obtained to contact for the follow-up appointment and/or to initiate study participation. These identifiers will be kept in a separate database on the secured OHSU network drive or on OHSU acceptable cloud storage location.

Participants will be given modest financial compensation for attending study visits and intervention sessions: $20 gift cards will be given at each study visit and post-intervention focus group interview (4 total), and $5 will be added for each intervention session attended (9 total) for a total possible compensation amount of $125 per participant. Compensation will be provided at the completion of each visit via ClinCard which will be reloaded following each visit. The amount compensated is comparable to the compensation provided in similar research studies and should adequately compensate for the time and travel involved without constituting undue pressure or influence on, or coercion of, the prospective research participants to volunteer for or continue participation in the research study.

Consent Process

Participants will be informed about their rights at the beginning of the telephone screening. The telephone screening confirms that adults are competent in reading and speaking English. It also confirms that adults are cognitively capable of consent through administration of the Telephone Interview for Cognitive Status. A HIPAA waiver of authorization (WOA) will allow for the collection of identifiable data before obtaining full consent in person. Information to be collected during screening are as follows:

Screening Measures
Abbreviated Posttraumatic Stress Disorder Checklist (PCL-6), depression (PHQ-9), suicidality (PHQ-9 item 9), substance use (Alcohol Use Disorders Identification Test; Cannabis Abuse Screening Tool; Fagerstrom Nicotine Dependence Scale), medical history, self-reported medication history, current mindfulness practice, historical mindfulness experience.
Demographics
Age, gender, sex, ethnicity, BMI, marital status, education, income, employment status, military branch, era of service, years enlisted.

Upon arrival at the research lab in Hatfield Research Center (HRC) for the first study visit, study personnel will review the study consent form with the participant and solicit questions. Once the subject verbally confirms understanding and interest in participation, they will be asked to sign consent forms and will be provided copies prior to leaving the HRC building. All research activities, including interventions, will take place at OHSU. Data collection and analysis will take place in the Oken Lab in OHSU's Hatfield Research Building, and interventions will take place at OHSU's Kohler Pavilion.

Subjects will be encouraged to ask questions throughout the duration of participation.

Modifications to the Consent Process

In this study, Veterans will primarily be recruited when they see a flyer and contact the study team. The PI will not be accessing the VA electronic medical record to identify a potential patient. Once a potential participant reaches out to the PI and study from the contact information provided in the flyer, the PI or a delegated study team member will review the initial phone script to understand if the participant meets eligibility and shows interest in participation. If the veteran is interested, the study team will call the participant at an agreed upon time to conduct screening procedures over phone. If the participant is eligible, the participant will be invited to sign the OHSU informed consent form prior to randomizing to the study intervention (MBSR or HWE).

We believe that requesting the participant to sign the consent form after screening will not adversely affect the patient as we will have a waiver to store this information in the secure network drive at OHSU. We have carefully selected the data elements as the minimum necessary in order to identify and recruit potentially eligible Veterans into this study without placing undue burden on the veterans. This is a minimal-risk study. Patients can avoid an unnecessary visit at OHSU to sign the consent form if they are ultimately determined to be not eligible after screening.

Non-English Speaking Subjects

English language reading and speaking are inclusion criteria for this study. Certain elements of the protocol such as the stressor task (Portland Arithmetic Stress Task) are not validated in other languages and would therefore not be able to be applied uniformly.

Assent of Children and Parent Permission

This is a study on Veterans so children will not be included.

Adults Unable to Consent/Decisionally Impaired

No decisionally-impaired adults will be recruited, and cognitive status will be determined during the phone screen.

6) Procedures

Aim 1 – Quantitative data: Recruitment and retention rates will be collected, compared between conditions, and evaluated in relation to previous research on MBSR recruitment and attrition. Correlations between rates of home practice completion (e.g., self-guided meditation practice) and attrition rates per condition will be examined for relationships. This quantitative data will be used to guide focus group prompt development.

Aims 1&2 – Qualitative data: Focus groups will be conducted in accordance with guidelines for maximizing impact of qualitative research in feasibility studies.[66] Broad topics will cover: 1) intervention content, 2) trial design and process (including stress induction and concurrent physiological data collection), 3) outcomes, and 4) measures. These discussion topics will be tailored to fit combat veterans with PTSD symptoms via consultation with the Veteran's Engagement Group (VEG; see *Human Subject Considerations* for a description of the VEG; see also Matsumoto LOS). A thematic analysis approach[67] will explore participant experiences to understand feasibility, acceptability, and impact of assessments, protocol, and interventions. Analysis process will consist of: 1) familiarization, 2) initial coding, 3) creating themes, 4) reviewing themes, 5) defining and naming themes, and 6) data interpretation. The PI will work with Dr. Christopher (co-mentor) who has experience conducting thematic analysis of qualitative data in feasibility studies, and a trained RA to independently review focus group data. Emerging themes will help develop a coding scheme that the team will apply independently the finalized code structure. The team will meet regularly to review coding and discrepancies to ensure inter-rater reliability.

Aim 2 – Physiological data: We will assess feasibility and effectiveness of stress induction by analyzing change in blood pressure (BP) between baseline and a cognitive stressor (see *Stress induction paradigm*

section below). BP will be collected via Caretaker Medical VitalStream™ device, which accurately and wirelessly measures vital signs. The VitalStream™ uses an automated readout inflatable finger cuff and is connected via Bluetooth to a tablet. Within-participants baseline-to-stressor task t-tests will evaluate feasibility of stress induction. Significant increases in BP from baseline to stressor will constitute effective stress induction. **Quantitative analyses will be conducted in SPSS v.28,[68] and qualitative will be conducted in NVivo.[69]**

Stress induction: **1. Baseline:** The Simple Reaction Task (SRT) will serve as a baseline for the stressor task. Participants press a key each time a number appears on the screen. The SRT has been used as a baseline for cognitive stressors in prior Oken lab studies; **2. Stress induction:** The Portland Arithmetic Stress Task (PAST)[70] is a cognitive stressor comprised of arithmetic problems titrated in difficulty. It has an adaptive failure algorithm, maintaining an error rate of ~40%. It has been shown to induce physiological stress across groups.[70-72]

Aim 3 – Quantitative data will be collected on paper and entered in REDCap by a study team member on an Oken lab computer and in-person clinical interview (i.e., Clinician-Administered PTSD Scale for DSM-5 [CAPS-5]). Using this data, we will examine sensitivity and responsiveness to change of outcomes. This Aim will be conducted in accordance with best practice guidelines,[73,74] CONSORT recommendations,[75] and previous research.[76,77] Sensitivity in both groups will be analyzed via relative efficiency; dividing the *F*-statistic for each physiological (systolic and diastolic BP) and self-report (psychological resilience and PTSD symptoms) by the largest *F*-statistic among outcomes (see Table below for measures).[77,78] This process will clarify which outcomes are most sensitive to MBSR. To generate *F*-statistics for relative efficiency, we will conduct repeated measures ANOVAs for each outcome in both groups. This statistical approach focuses on the degree to which measures are sensitive, not whether change is significant. Responsiveness to change over time will be assessed in the MBSR group for physiological and self-report outcomes by: 1) calculating and comparing standardized mean response by subtracting baseline mean response from post-intervention mean response, and dividing by standard deviation of change[74,79,80] and 2) examining zero-order correlations between a global impression of change measure (post-intervention) and change scores (baseline to post-intervention) for self-report outcomes.[81-83]
Primary measures to be collected are listed below:

Method	Variable	Measurement Tool	Timepoints
Paper>REDCap	Psychological resilience	Brief Resilience Scale (BRS)	Pre, mid, post
Paper>REDCap	PTSD symptoms	PTSD Symptoms Checklist for DSM-5 (PCL-5)	Pre, mid, post
Paper>REDCap	Mindfulness	Five Facet Mindfulness Questionnaire (FFMQ-15)	Pre, mid, post
Paper>REDCap	Perceived stress	Perceived Stress Scale (PSS-10)	Pre, mid, post
Paper>REDCap	Loneliness	UCLA Loneliness Scale	Pre, mid, post
Paper>REDCap	Distress	Distress tolerance scale	Pre, mid, post
Clinical interview	PTSD symptoms	Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)	Pre, mid, post
CareTaker™	Physiological resilience	Blood pressure (BP)	Pre, mid, post

Stress induction: **1. Baseline:** The Simple Reaction Task (SRT) will serve as a baseline for the stressor task. Participants press a key each time a number appears on the screen. The SRT has been used as a baseline for cognitive stressors in prior Oken lab studies; **2. Stress induction:** The Portland Arithmetic Stress Task (PAST)[70] is a cognitive stressor comprised of arithmetic problems titrated in difficulty. It has an adaptive failure algorithm, maintaining an error rate of ~40%. It has been shown to induce physiological stress across groups.[70-72]

Interventions:
Mindfulness-Based Stress Reduction consists of weekly two-hour sessions for eight weeks, and a 7 hour retreat after Lab visit 3/week 8. The MBSR intervention will be facilitated by an experienced and

certified MBSR teacher. MBSR curriculum strongly encourages completion of home practice assignments (~30 minutes daily) to help integration of concepts into daily life. Participants will receive audio CDs and a DVD to help guide home practice**.**

Health and Wellness Education (HWE) Intervention is a didactic-based group intervention designed as an active comparator for randomized-controlled trials of MBSR. HWE provides instruction to participants regarding improving their emotional and physical health. In contrast to MBSR, there are no attempts to train participants' breathing, movement, or meditation habits or practices. HWE is administered in 8 weekly 2.5-hour classes with home practice to be completed between sessions (matched to MBSR for amount and effort). HWE also features one extended 7hour retreat, similar to MBSR.[84] Dr. Autumn Gallegos (consultant) has conducted trials of MBSR among veterans with PTSD using a control group based on similar materials, and will provide mentorship to the PI in administering the control intervention. Dr. Kaplan and a trained RA will facilitate HWE.

CareTaker VitalStream™. The CareTaker VitalStream™ is comprised of a lightweight wrist pack attached via Velcro, which is connected via thin tube to a small Velcro finger cuff that contains a low-pressure sensor. All materials used in the VitalStream™ are medical grade. VitalStream™ measures continuous pulse pressure waveforms for processing via Pulse Decomposition Analysis™ (PDA™). The PDA™ technology includes algorithms to calculate and continuously monitor hemodynamic-related parameters by analyzing reflective pulsewave morphology within the arterial system. The VitalStream™ allows for secure wireless monitoring via a real-time mobile application, or remote monitoring via a Cloud Portal. For the purposes of the study, we will monitor participant data via mobile application on an encrypted Android tablet in a room adjacent to the testing room during the laboratory stressor task. Dr. Kaplan (PI) designed and executed a pilot RCT using a previous version of CareTaker. Through this study Dr. Kaplan gained familiarity with the equipment and software, and developed relationships with key CareTaker Medical personnel.
Blood pressure. The VitalStream™ measures and records systolic, diastolic, and mean arterial pressure (MAP) using FDA-approved PDA™ technology. These algorithms have been validated in comparison to invasive central aortic measurement.
Heart rate. The VitalStream™ measures heart rate via low-pressure finger sensor, with accuracy validated in comparison to 3-lead ECG measurement.
Respiration rate. The VitalStream™ accurately measures respiration rate (breaths per minute) non-invasively by extrapolating pulsewave morphology via PDA™. The VitalStream™ calculates respiration rate in this fashion with equivalent accuracy to ECG-derived respiration using a 3-lead ECG electrode.

Potential participants will be sent a MyChart recruitment invitation and a follow-up (as applicable) via an email notification, as below, with the Subject "New Research Study" instructing them to log into MyChart to learn more and respond. The text of this invitation is included in the eIRB submission. The link in the MyChart invitation will take the potential participant to their MyChart homepage with a link to a description of the study. Potential participants will express interest or decline by pressing the associated buttons in MyChart, or they will not respond. If the potential participant indicates interest, they are automatically associated to the study in Epic with a status of "interested;" the study remains listed on the patient's Research Studies page in MyChart, and the study team immediately receives an in-basket notification in Epic so that they can follow up with the patient. If the patient clicks "No, Thank You" this study will no longer appear on their Research Studies page in MyChart, and the patient is automatically associated to the study in Epic with a status of "declined." When the participant expresses interest, the study team will call the participant to schedule the initial phone call for an initial review of eligibility and a second screening phone call before the participant is enrolled on study. Details of the initial and second phone call are included under "recruitment methods" section.

Please see below for a description of the study schedule. All survey data will be captured in paper surveys from study participants and will be directly entered in the REDCap database by a study team member.

Study Schedule:

Visits	Initial phone call 1	Screening phone call	Lab visit 1	Wk 1[e]	Wk 2	Wk 3	Wk 4	Wk5/ Lab visit 2	Wk 6	Wk 7	Wk8/ Lab visit 3	Retreat	Post-intervention Wk9
Study overview and eligibility review	X												
Screening questionnaires[a]		X											
Demographics [b]		X											
Informed consent			X										
MBSR/HWE[d] intervention				X	X	X	X	X	X	X	X	X	
Study Visit Questionnaires[c]			X					X			X		
Clinical interview (Clinician administered PTSD scale for DSM-5 (CAPS-5)			X					X			X		
CareTaker VitalStream™ (physiologic data collection, BP)			X					X			X		
Lab Stressor			X					X			X		
Focus group Qualitative interview													X
Approximate total time	15 mins	30 mins	120 mins	150 mins	150 mins	150 mins	150 mins	270 mins	150 mins	150	270 mins	7 hours	120 mins

a. Screening measures will include: PTSD (PCL-5), depression (PROMIS), suicidality (PHQ-9), substance abuse (Alcohol Use Disorders Identification Test, Cannabis Abuse Screening Tool, Fagerstrom Nicotine Dependence Scale) in addition to review of eligibility
b. Demographic information includes age, gender, sex, ethnicity, BMI, marital status, education, income, employment status, military branch, era of service, years enlisted. Medical and medication history, current and historical mindfulness experience are captured during screening
c. Questionnaires include Brief Resilience Scale, PTSD Symptoms Checklist for DSM-5 (PCL-5,6), UCLA Loneliness Scale, CAPS-5, Five Facet Mindfulness Questionnaire (FFMQ-15), Perceived Stress Scale (PCL-10), Distress tolerance scale (DTS)
d. Participants are randomized at visit 1 to either MBSR or HWE. All participants have 30-minute practice assignments to be carried out every day at home.
e. Week 1 of the interventions will occur within one week of completing Lab Visit 1 for all participants.

Participants may be withdrawn from this study without their consent in order to protect them from excessive risk (e.g., if they demonstrate unsafe elevated blood pressure), or in order to maintain the integrity of the study and data (e.g., a participant is not following study procedures and/or may be deliberately providing false information).

7) Data

Handling of Data

Data collected will include computer-based and physiological recordings listed above, as well as demographic data such as age and gender. Data will also include health status information, such as

medical conditions and prescription medications for use in determining eligibility. All data will be stored on a restricted OHSU network drive in a limited access folder or in a REDCap database, and the study PI and designee will be responsible for storage and transmission of the data. Following this study, all data will be transferred and stored indefinitely in repository IRB #7436. No specimens will be collected as part of this study.

a) Sharing of Results with Subjects

Participants will be given the opportunity to view their heart rate and blood pressure when it is taken in the lab during the baseline condition, unless they would prefer not to. Participants will not be shown their physiological data during the stressor condition due to the expected increases resulting from cognitive stress. Besides this, participants will not have access to any other data collected as a part of this study. If participants demonstrate pathological blood pressure during the course of the study, they will be notified and referred to their PCP and/or urgent care. If blood pressure reaches hypertensive crisis (180/110) the participant will be referred immediately to the emergency department. No data will be used for clinically decision-making, nor will it be entered into participants' medical records. Referrals will be made based on generic critical blood pressure values only.

b) Data and Specimen Banking

If data or specimens will be banked in a repository for future use as part of this protocol submission, describe here (or in a separate repository protocol document) where they will be stored, how long they will be stored, how they may be accessed, and who will have access to the specimens. Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Data will be sent to a repository maintained separately from this study. They will be stored indefinitely in repository IRB #7436. Participants will be requested to consent to sharing data in the repository which will be optional. The repository investigator and members of the Oken Cognitive Neuroscience Laboratory are allowed to access the data and will have requisite HIPAA and other trainings. Please see repository protocol for details related to that study.

8) Data Analysis

Quantitative data:

Recruitment and retention rates will be collected, compared between conditions, and evaluated in relation to previous research on MBSR recruitment and attrition. Correlations between rates of home practice completion (e.g., self-guided meditation practice) and attrition rates per condition will be examined for relationships.

Within-participants baseline-to-stressor task t-tests will evaluate feasibility of physiological stress induction. Significant increases in BP from baseline to stressor will constitute effective stress induction.

Sensitivity in both groups will be analyzed via relative efficiency; dividing the F-statistic for each physiological (systolic and diastolic BP) and self-report (psychological resilience and PTSD symptoms) by the largest F-statistic among outcomes (see Table above for measures).[77,78] This process will clarify which outcomes are most sensitive to MBSR. To generate F-statistics for relative efficiency, we will conduct repeated measures ANOVAs for each outcome in both groups. This statistical approach focuses on the degree to which measures are sensitive, not whether change is significant. Responsiveness to change over time will be assessed in the MBSR group for physiological and self-report outcomes by: 1) calculating and comparing standardized mean response by subtracting baseline mean response from post-intervention mean response, and dividing by standard deviation of change[74,79,80] and 2) examining zero-order correlations between

a global impression of change measure (post-intervention) and change scores (baseline to post-intervention) for self-report outcomes.[81-83]

Qualitative data:
A thematic analysis approach[67] to qualitative data will explore participant experiences to understand feasibility, acceptability, and impact of assessments, protocol, and interventions. Analysis process will consist of: 1) familiarization, 2) initial coding, 3) creating themes, 4) reviewing themes, 5) defining and naming themes, and 6) data interpretation.

9) Privacy, Confidentiality and Data Security

Standard institutional practices will be followed as described in the OHSU Information Security Directives (http://www.ohsu.edu/xd/about/services/integrity/policies/ips-policies-info-sec-directiv.cfm#results) to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures. Any staff that will be involved in these research activities will have completed the requisite Human Subject Protection Training as required by the IRB prior to engagement. Documentation of training will be held on secure password protected computers at OHSU. Prior to implementation of any protocol changes, amendments will be submitted to the OHSU Institutional Review Board for approval. Dr. Kaplan will be responsible for continuous data and safety monitoring of all participants, and discussion of any data or safety monitoring concerns will be a routine topic of mentorship and consultation meetings. In the event there are AEs/SAEs that require medical intervention, Dr. Oken, a board-certified neurologist, will be available to review events and refer them as needed.

Paper files will be stored in locked filing cabinets in restricted access offices at OHSU and will not leave the Oken lab facility. Electronic data is stored on restricted drives on the OHSU network, on OHSU approved cloud location and on encrypted computers. Electronic data will also be stored in a custom database housed on an OHSU secure server. Access to data is restricted to study personnel. Access to data requires OHSU ID/password authentication.

Upon enrollment, participants will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files for data analysis will contain only the subject code. Codes will not contain any part of the 18 HIPAA identifiers (initials, DOB, MRN) The key associating the codes and the participants personally identifying information will be restricted to the PI and study staff. The key will be kept secure on a restricted OHSU network drive in a limited access folder.

BP will be collected via Caretaker Medical VitalStream™ device, which accurately and wirelessly measures vital signs. The VitalStream™ uses an automated readout inflatable finger cuff and is connected via Bluetooth to a tablet. The CareTaker™ is completely wireless, and will relay data via Bluetooth connectivity to a tablet. It allows for secure wireless monitoring via a real-time mobile application, or remote monitoring via a Cloud Portal. For the purposes of the study, we will monitor participant data via mobile application on an encrypted Android tablet in a room adjacent to the testing room during the laboratory stressor task. There is no storage, processing or transmission of any PHI or HIPAA identifiers through VitalStream. It does not connect to OHSU network, but is transmitted via Bluetooth to an encrypted tablet.

At the completion of the study, if patients consent to sharing data in the repository, their data will be released to repository IRB #7436. See repository protocol for details about requesting, releasing, and labeling data.

10) Risks and Benefits

a) Risks to Subjects

The risk in participating in the present study is low. Participants may feel distress when reporting their PTSD symptoms or identifying their index trauma (i.e., the most salient trauma connected to their PTSD symptoms) as part of the administration of the Clinician-Administered PTSD Scale (CAPS-5). Participants may also feel discomfort or embarrassment when discussing their general experiences during the intervention conditions. They may also feel stress or frustration when completing the laboratory stressor paradigm. Participants have the right to withdraw, and may attend intervention groups and not actively participate, or may not complete MBSR home practice between sessions.

There is no discomfort associated with the collection of physiological data. The CareTaker™ device using a Velcro finger cuff attached with similar tightness to an arm cuff blood pressure monitor. A thin clear tube connects the finger cuff to a small wrist pack that houses the electronic components of the device. The CareTaker™ is completely wireless, and will relay data via Bluetooth connectivity to a tablet.

One of the potential risks of participation breach of confidentiality. It is possible that, if someone inadvertently obtained data, this could result in harm to research participants, with legal, financial, or emotional implications of the affected Veterans. We will take all possible measures to protect the security and integrity of personal health information.

b) Potential Benefits to Subjects

Veterans may find it rewarding to engage in group-based interventions in which they are encouraged to share their experiences with other veterans with similar struggles related to PTSD symptoms. They may similarly appreciate being able to share their perspectives regarding their ability and strategies for coping with symptoms. Participants may also experience reduction in symptoms of PTSD, depression, and anxiety as a result of participating in the MBSR condition.

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