PROTOCOL TITLE:
Brain and Meditation (BAM) Study

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GRANT TITLE:
Neurobiological mechanisms of perceived stress and their modification through behavioral intervention

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1.2	12/10/2021	Clarified use of GPS data	Yes
2.0	01/28/2022	Updates to screening procedures, clarification of eligibility criteria, updates to compensation section, and addition of Qualtrics to the data management and confidentiality section	Yes
3.0	03/21/2022	Added ClinicalTrials.gov ID, added 3 surveys to the "Schedule of study procedures" table (Payment Information Survey, Payment Information Update Survey, & Feedback Survey), added procedures to withdraw participants who do not complete Timepoint 1 (Initial Activities)	Yes
4.0	05/12/2022	Updated amount of time it takes to complete each timepoint in section **13.3 Research Procedures**; added that certain survey items are required to be completed to sections **17.3 Steps to make participants feel at ease** & **22.6 Minimizing risks**	Yes
5.0	10/12/2022	Clarified that we will continue to use data collected by the Healthy Minds Program app until Timepoint 6 (3-Month Follow-Up) in section **13.5 Long-term follow-up**	Yes
6.0	2/28/2023	Clarified that any clinical research personnel can provide support for adverse responses in section **22.6 Minimizing risks**	
7.0	10/17/2023	Removed the MRI substudy from the protocol.	Yes

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1.0 Study Summary

Study Title	Brain and Meditation (BAM) Study
Brief Summary	This study is a randomized controlled trial to test the impact of an app-based meditation program on perceived stress and behavioral and brain correlates of stress. Healthy adult participants between the ages of 25-65 will be enrolled in the study for about 4-5 months.
Number of study sites	1
Study Design	Participants will be randomized into one of two groups: the intervention group or the waitlist control group. The intervention group will use a mobile health app for four weeks. Participants will complete pre-intervention, weekly, post-intervention, and 3-month follow-up surveys and tasks.
Primary Objective	Test for hypothesized group differences in perceived stress and hippocampal-dependent behavior following participation in a 4-week meditation program.
Secondary Objective(s)	Within the meditation group, determine whether reductions in perceived stress are associated with changes in hippocampal-dependent behavior.
Research Intervention(s)/ Investigational Agent(s)	Healthy Minds Program (HMP) – a mobile health meditation training program
Drugs/devices used on study (including any IND/IDE #)	Healthy Minds Program (HMP) – a mobile health meditation training program
Study Population	25-65 year old healthy adults with no significant experience with meditation
Sample Size	150 participants
Study Duration for individual participants	4-5 months
Study Specific Abbreviations/ Definitions	mHealth = mobile health HMP = Healthy Minds Program

2.0 Background

2.1 Relevant prior experience and gaps in current knowledge

Meditation training is known to reduce subjective appraisals of stressful life events, or "perceived stress", but access to in-person programs is limited due to high costs and lack of available services. The hippocampus is a brain region highly sensitive to stressful and adverse life events, and may play a mechanistic role in determining individual differences in perceived stress, a hypothesis that is best tested using an intervention with stress-reducing effects. This project will address each of these current knowledge gaps by studying the impact of a 4-week mobile health (mHealth) meditation training program on perceived stress and hippocampal-dependent behavior.

2.2 Relevant preliminary data

We have conducted similar mHealth studies with educators in Wisconsin (IRB Protocol: 2020-0533) and undergraduate students at UW-Madison (IRB Protocol: 2020-1454). Both studies provided evidence that a large number of participants are willing to download and regularly use the Healthy Minds Program (HMP) app as well as stay engaged in a longitudinal study. We have also identified correlations between elevated perceived stress and compromised hippocampal-dependent behavior in cross-sectional data.

2.3 Scientific background for, rationale for, and significance of the research

Meditation training dramatically reduces perceived stress and has benefits for psychiatric conditions associated with elevated perceptions of stress, such as depression and post-traumatic stress disorder (PTSD). Access to in-person programs, however, is limited due to associated cost and lack of available services.

Research on behavioral and neurobiological mechanisms contributing to individual differences in perceived stress is largely limited to correlational, cross-sectional studies. The inclusion of behavioral outcomes in research on a meditation training program will allow us to draw causal inferences regarding mechanisms of perceived stress.

Prior research has demonstrated that greater roaming entropy, or more diverse activity around one's lived environment, is associated with greater psychological well-being in humans (Heller et al., 2020) and with greater neurogenesis in the hippocampus of laboratory mice. We are interested in examining whether a meditation intervention that seeks to improve well-being will do so in part through effects on greater roaming entropy, and whether individual differences in roaming entropy (either at baseline, or in response to the meditation intervention) are associated with behavioral changes consistent with greater hippocampal neurogenesis.

In this project, we will conduct a randomized controlled trial of the HMP vs. waitlist control to test the efficacy of a fully remote, 4-week meditation intervention on reducing perceived stress in a healthy adult population. Using behavioral measures with a known neurobiological basis (pattern separation and real-world exploratory behavior), we will investigate hypothesized mechanisms associated with individual differences in perceived stress and how they may be impacted by meditation training.

3.0 Study Objectives and Endpoints

3.1 Specific aims

- To assess efficacy of a 4-week mHealth meditation training program on reducing perceived stress.
- To investigate the effects of meditation training on candidate behavioral and brain mechanisms of perceived stress: behavioral pattern separation and real-world experiential diversity.
- To assess the extent to which lower levels of perceived stress following mindfulness training is associated with corresponding changes to these candidate mechanisms.

3.2 Hypotheses

- Intervention participants will show larger reductions in perceived stress relative to waitlist control participants at post-intervention and follow-up timepoints.
- Intervention participants will show improved pattern separation behavior relative to waitlist control participants at post-intervention and follow-up timepoints.
- Intervention participants will show increased real-world "experiential diversity" assessed using GPS location tracking relative to waitlist control participants at post-intervention and follow-up timepoints.
- Changes in hippocampal-dependent behavior will be correlated with reductions in perceived stress.

3.3 Primary and secondary study endpoints

Primary endpoints

- Scores on the perceived stress scale at post-intervention (T5) controlling for baseline (T1)

Secondary endpoints

- Performance on the behavioral pattern separation task *(post-intervention and follow-up/T6)*
- PROMIS depression and anxiety *(post-intervention and follow-up)*

Tertiary and exploratory endpoints

- Symptoms of PTSD measured using the PCL-5 *(post-intervention and follow-up)*
- PROMIS sleep disturbances *(post-intervention and follow-up)*
- Five-facet mindfulness questionnaire, awareness subscale *(post-intervention and follow-up)*
- NIH toolbox Loneliness *(post-intervention and follow-up)*
- Healthy Minds Index *(post-intervention and follow-up)*
- Real-world experiential diversity measured using continuous GPS location tracking *(Measured continuously throughout study participation)*
- Trajectories of change for self-report outcomes assessed on a weekly basis

4.0 Number of Participants

4.1 Total number of participants
This study will enroll 150 participants at UW-Madison.

4.2 Number of participants expected to be enrolled and screened vs. number of participants needed to complete the study
N/A - Only eligible participants will be enrolled in this study. Participants will be screened prior to enrollment.

4.3 Criteria for "enrolled" participants and replacing withdrawals
Participants will be considered enrolled after signing the consent form. If participants leave the study prior to randomization, they will be replaced. However, participants who leave the study after being randomized will not be replaced.

5.0 Inclusion and Exclusion Criteria

5.1 Screening
After reading a description of the study, individuals who are interested in participating will complete an Online Eligibility Survey in REDCap. The survey will automatically inform individuals who do not meet eligibility criteria for auto-exclusion items that they are not eligible. Other items will be reviewed by study staff to determine eligibility. We will review those responses and inform potential participants about their eligibility via email. We will retain all screening data to maintain a record of reasons individuals are not eligible for the study.

5.2 Inclusion criteria
- 25 to 65 years old
- Individual can read, write, speak, and understand English
- Able to provide informed consent
- Willing and able to complete all study procedures, including the Healthy Minds Program
- Has access to an Android or iPhone (Apple/iOS) smartphone that can download apps from Google Play or the Apple App Store
- For payment purposes, must be a US citizen or a permanent US resident (green card holder)

5.3 Exclusion criteria
- Extensive experience in meditation practice (e.g., regular daily meditation practice for the past 6 months or regular weekly meditation practice for the past 12 months), experience in substantively similar meditation training programs (e.g., attended a meditation retreat or a yoga/body practice retreat with a significant mediation component), or substantial previous use of the Healthy Minds Program app
- Individuals will be excluded if they previously participated in substantively similar research at our Center at the discretion of the investigator due to similar tasks being used in certain studies

- History of psychosis
- History of mania
- Current psychopathology that interferes with study participation

5.4 Specific population
This study will include a sample of adults between 25 and 65 years old that is demographically representative of the overall population of the United States. We will exclude individuals under age 25 and over age 65 due to age-related differences in the brain regions we are studying. Young people (under age 25) have brains that are still developing, while older people (over age 65) are expected to start showing age-related hippocampal decline and behavioral changes that would confound our ability to test hypotheses related to stress and the hippocampus.

6.0 Special Populations

6.1 The study will not enroll individuals from any of the following populations. However, pregnant women may be incidentally enrolled. We will not be screening for pregnancy because there are no known additional risks to pregnant persons or fetuses from study procedures/intervention. This study involves activities that are of no greater risk than typical activities of daily living. Assessments will be conducted entirely on a smartphone or other digital device and consist of completing questionnaires about health and well-being, completing a memory task, and passive location tracking. The intervention is smartphone-based and consists of listening to podcast-style lessons about well-being and completing meditation practices. We have chosen research activities that minimize time and burden for participants that are similar to typical activities encountered in daily life; therefore, any risk involved is minimal. There is no reasonable expected risk of the study procedures/intervention on pregnant women or fetuses, so preclinical studies are not scientifically appropriate. Additionally, this research is unrelated to decisions regarding termination of pregnancy and viability of a neonate.

- ☐ Children/Minors
- ☐ Pregnant persons / fetuses
- ☐ Prisoners
- ☐ Participants with impaired decision-making capacity

6.2 The study will not enroll individuals from any of the following populations.

- ☐ Non-English speaking participants
- ☐ Illiterate or Low Literacy participants
- ☐ Participants with visual or hearing impairments
- ☐ Status Relationship: Individuals with a status relationship with the PI or other study team members (e.g., employees, students, family members)

6.3 The study will not specifically target enrollment of individuals from any of the following populations. However, we will not ask questions about every category (e.g., veterans/military personnel), and may, therefore, unknowingly enroll individuals who belong to some of the following populations.

- ☐ Individuals who are receiving inpatient or outpatient services for mental illness, developmental disability, or alcohol and other drug abuse (AODA)
- ☐ Individuals who are protectively placed by a court in a treatment facility
- ☐ Veterans/Military Personnel
- ☐ Emancipated minors
- ☐ Anyone especially vulnerable to manipulation or inducements for participation as a result of their illness or socioeconomic condition

7.0 Recruitment Methods

7.1 Sources of participants

We will recruit from an ongoing companion study (PI: Richard Davidson; Title: "Individual differences in affective chronometry"; IRB Protocol: 2018- 0937), the community, research recruitment services, and the Participant Registry at the Center for Healthy Minds (IRB Protocol: 2019-0330).

7.2 Identifying participants

Research candidates will self-identify in response to advertisements, such as flyers, website ads (e.g., on the Center for Healthy Minds website, Craigslist, and/or other relevant websites), email ads, and ads on research recruitment services (e.g., Prolific). Another method of recruitment will be contacting participants from the ongoing companion study who have expressed interest in other research studies. It will be made clear that this intervention study is separate from the companion study and that participation is fully voluntary. We will recruit these individuals based on whether they self-identified as having interest in other studies. Finally, we may recruit individuals from the Participant Registry at the Center for Healthy Minds who previously indicated interest in being contacted about research studies.

7.3 Recruitment method

Recruitment efforts will take place only during the recruitment phase. All advertisements will be removed once recruitment is complete. We may post flyers at various local businesses (e.g., libraries, stores, and restaurants) every few months during the recruitment phase, post website advertisements at the beginning of recruitment and remove the ads when recruitment is completed, and contact individuals through research recruitment services. We may make up to 3 attempts to contact participants from the companion study by email and/or phone with a brief description of the opportunity. We may contact individuals from the Center for Healthy Minds Participant Registry one time via email with information about the research opportunity.

7.4 Recruitment materials

We will use email advertisements, flyers, research recruitment services, and website advertisements to inform potential participants about the study. Recruitment will occur on a continuous basis during data collection.

7.5 Compensation

We will pay participants by sending checks or prepaid debit cards in the mail. Participants will be paid twice during the study – once after completion of the Week 4 Activities and again after

completion of the 3-Month Follow-Up. If participants choose to withdraw or are withdrawn by the study team, they will receive payment for the study components that they completed.

Participants will be compensated up to $150 for participating in the study as follows:

- Initial (Pre-Intervention) Activities = $10
- Week 1 Activities = $10
- Week 2 Activities = $10
- Week 3 Activities = $10
- Week 4 (Post-Intervention) Activities = $25
- 3-Month Follow-Up = $45
- Daily Movement (Location Tracking; must provide at least 60 days of valid data) = $10
- Bonus for Completing All Study Procedures = $30

8.0 Consent/Assent Process

8.1 Informed consent process

To obtain consent we will follow HRP-090 - SOP - Informed Consent Process.

Online Eligibility Survey Consent Process: Research candidates will be provided with an Information Sheet prior to completing the Online Eligibility Survey in REDCap. After reading the Information Sheet, research candidates will check a box to indicate that they have read the information and would like to continue with the survey. Survey data will be stored on REDCap and on a password-protected secure server.

Consent Process:

1. We will email (or mail, upon request) a consent form to research candidates who are potentially eligible for the study after completing the Online Eligibility Survey. We will ask participants to review the consent form prior to completing the Phone Screen (for MRI substudy participants) or Study Consent Call (for non-MRI substudy participants).
2. Eligible research candidates will be consented over the phone or via a web conferencing tool (e.g., Zoom) either during a Study Consent Call or immediately after the Phone Screen by trained research staff (i.e., principal investigator, study coordinator, or research assistant). We will recommend that participants complete the Phone Screen and/or informed consent process in a private room, if possible. If eligibility is not established upon completion of the Phone Screen, we will set up a separate time to call participants over the phone or by web conference to complete the informed consent process once eligibility is determined.
3. During the Study Consent Call, we will verify the research candidate's identity, review the consent form, and ask the research candidate if they have any questions or need further clarification about any aspects of the study. We will let research candidates know that they do not need to make a decision about participation right away, but can let us know once they have decided. We will inform research candidates that participation is voluntary and that they can stop at any time or skip any portion of the study that they do not feel comfortable completing. We will ensure that participants know who to contact if they have questions or concerns about the study in the future. We are requesting a waiver

of signed consent for both the non-MRI and MRI substudies. If a research candidate chooses to continue with participation, we will document that the participant has given oral consent prior to starting study procedures.

4. If circumstances arise that make it necessary to obtain re-consent of research participants (e.g., substantive changes in the research, significant new findings), we will email the updated consent form with changes highlighted to the participant and explain the changes either over the phone or via a web conferencing tool (e.g., Zoom. We will ask participants if they have any questions/concerns. If they would like to continue in the study, we will document that the participant has given oral consent prior to continuing with the study.

8.2 Altering elements of consent

We are requesting an altered consent process and waiver of signed consent for the Online Eligibility Survey and Phone Screen, which present no more than minimal risk of harm to subjects and involve no procedures for which written consent is normally required outside of the research context. The Online Eligibility Survey and Phone Screen will be used to determine if research candidates are eligible for the study. The forms ask questions for screening purposes only, such as age, English proficiency, meditation experience, general health issues, and psychiatric symptoms.

The Online Eligibility Survey could not be carried out without the waiver because meeting with all research candidates who respond to our ads to obtain written informed consent would not be practical. Also, providing more information may decrease understanding of consent information and/or reduce study enrollment. If we provided all elements of consent in the Online Eligibility Survey, research candidates may not read all the information and be uninformed, or they may not sign up for the study at all. We would like to provide the essential elements of consent while reducing subject burden as much as possible.

We are requesting a waiver of signed consent for the study, which presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. We will provide participants with a long form consent document that they can review and keep, complete a Study Consent Call over the phone/Zoom, and obtain oral consent, which we will document in our records prior to starting study procedures.

9.0 Process to Document Consent in Writing

9.1 Documentation of consent

Because this is a remote study, we will not follow HRP-091 - SOP - Written Documentation of Consent. Participants will not provide written consent. Instead, they will provide oral consent over the phone/Zoom, which we will document on the Oral Consent Script.

9.2 Waiver of written documentation of consent

We are requesting a waiver of signed consent for the Online Eligibility Survey and Consent Form, which present no more than minimal risk of harm to subjects and involve no procedures for which written consent is normally required outside of the research context.

For the Online Eligibility Survey, research candidates will be provided with an Information Sheet in REDCap prior to completing the survey. After reading the Information Sheet, research candidates will check a box to indicate that they have read the information and would like to continue with the survey.

We will provide participants with a copy of the consent form and will obtain oral consent over the phone/Zoom prior to starting study procedures. We will document that the participant has provided consent on the Oral Consent Script.

10.0 Setting

10.1 Location

Research procedures will be performed remotely and at the Center for Healthy Minds.

11.0 Study Intervention

11.1 Description

The study intervention is the Healthy Minds Program (HMP), a 4-week mobile health meditation training program. HMP was developed by our affiliated non-profit, Healthy Minds Innovations, Inc. Participants in the intervention group will download a study-specific version of the HMP app to their smartphone and complete the 4-week program. Participants in the waitlist control group will be given the opportunity to use the HMP app upon completion of the study.

12.0 Study Timelines

12.1 Study timeline

Participants will be involved in the study for approximately 4-5 months. Recruitment will start upon UW Institutional Review Board (IRB) approval and continue until study goals are reached. We estimate that we will complete the study, including primary analyses, in approximately 3 years.

13.0 Procedures Involved

13.1 Study design

This will be a two-group randomized controlled trial assessing the impact of the Healthy Minds Program (HMP), a meditation-based well-being app, on behavioral and self-reported outcomes associated with stress and well-being in 150 individuals. Participants will be adults ages 25 to 65

years who have no significant experience with meditation, have access to a smartphone, and are willing to follow through on all aspects of the protocol. The primary endpoint will be scores on the perceived stress scale. Participants will be randomized to the HMP or waitlist control group at a 2:1 ratio. Prior to randomization, participants will complete initial surveys and a computerized task remotely. Participants assigned to the HMP group will complete a 4-week well-being program remotely using an app on their smartphone. Each week participants will also complete a set of online surveys/tasks. Waitlist control participants will also complete the online surveys/tasks each week for 4 weeks. All participants will complete a final set of follow-up surveys/tasks 3 months later. In addition, we will track participant location using GPS smartphone technology throughout the study.

13.2 Schedule of study procedures

Study Procedure/Activity	Web Screen	Phone/ Zoom Call	T1	4-Week Intervention		T6
				T2-T4	T5	
Consent via Information Sheet	X					
Screening Questions	X					
Review Eligibility	X					
Informed Consent Process for Main Study		X				
Payment Information Survey		X				
Payment Information Update Survey						X
Intervention (i.e., Healthy Minds Program)				X[1]	X[1]	
Behavioral Pattern Separation Task			X		X	X
Attention Check Items			X		X	X
Behavioral Risk Factor Surveillance System (BRFSS) Adverse Childhood Experiences (ACE) Module			X			
Demographics			X			
Demographics & Meditation Experience			X			
Determinants of Meditation Practice Inventory-Revised (DMPI-R)			X			
Digital Working Alliance Inventory (DWAI)				X[1]	X[1]	
Feedback Survey			X	X	X	X
Five Facet Mindfulness Questionnaire (FFMQ), Awareness Subscale			X		X	X
Flourishing Measure			X		X	X
Global Physical Activity Questionnaire (GPAQ)			X		X	X

Healthy Minds Index (HMIndex)			X		X	X
Mainz Inventory of Microstressors (MIMIS)			X		X	X
Marlowe-Crowne Social Desirability Scale (MCSDS)			X			
Mindfulness-Based Program - Meditation-Related Adverse Effects Scale (MBP-MRAES)					X[1]	
Mindfulness Adherence Questionnaire (MAQ)				X[1]	X[1]	X[1]
NIH Toolbox Loneliness			X		X	X
Pre- & Post-Practice Items				X	X	
PROMIS Item Bank - Emotional Distress - Anxiety (Computer Adaptive Version)	X		X	X	X	X
PROMIS Item Bank - Emotional Distress - Depression (Computer Adaptive Version)	X		X	X	X	X
PROMIS Item Bank - Emotional Distress - Sleep Disturbance (Computer Adaptive Version)			X	X	X	X
Perceived Stress Scale (PSS)			X	X	X	X
PTSD Checklist (PCL-5)			X		X	X
Location Tracking with Passive GPS[4]			X[2]	X[2]	X[2]	X[2]
Debriefing Form						X

[1]HMP group only
[2]Location Tracking collected continuously throughout the study

13.3 Research procedures

For this study, participants will complete tasks remotely, including online surveys and computerized tasks, the Healthy Minds Program (if assigned to the HMP group), and location tracking using a GPS app downloaded to participants' phones. We plan to enroll 150 participants.

Location Tracking: Throughout the study we will track participant location using GPS smartphone technology, which allows smartphones to automatically and passively (no participant input needed) capture information about the participant's activity (e.g., if the person is walking, remaining stationary, or moving at a rapid speed). After providing informed consent, participants will be oriented to the mobile phone application and will be instructed on downloading, installing, and optimizing the smartphone application required for participation. Real-world data collection will occur for approximately 4-5 months, from the time of consent until the 3-Month Follow-Up. Participants will be asked to keep their phone with them and powered on as much as possible during the study. The smartphone application will use an activity classifier program to determine if the user is remaining stationary, walking, or driving based on how quickly Wi-Fi and GPS signals change and on the strength of motion detected by the accelerometer. During the

3-Month Follow-Up (or if a participant discontinues the study), we will instruct participants on disabling the location tracking app.

Timepoint 1 - Pre-Intervention Activities: Participants will complete pre-intervention online surveys and tasks remotely using the REDCap system (see section **13.2 Schedule of study procedures** for measures that will be administered). Timepoint 1 will take 30 to 45 minutes. Survey and task completion will be self-paced, but we will ask participants to complete these activities within one week of receiving the REDCap link. Participants who do not complete the Timepoint 1 activities within one week may be unenrolled from the study.

Participants will complete a behavioral pattern separation task during Timepoints 1 (Pre-Intervention), 5 (Post-Intervention), and 6 (3-Month Follow-Up). During this task, participants will encode pictures of common objects while performing a basic categorization task. Participants will then label pictures as "Old" (targets, identical objects to those in the encoding phase), "New" (foils, or completely novel objects), or "Similar" (lure items, distinct exemplars of objects seen during encoding). We will calculate indices of correct differentiation of similar lures from identical targets ("pattern separation") and correct identification of targets that were previously presented ("recognition memory").

Intervention: Participants will be randomly assigned to one of two groups - approximately two-thirds to the HMP group and approximately one-third to the waitlist control group. Randomization will be done in REDCap; a REDCap email informing of group status will be sent to participants immediately after randomization. Participants will be stratified by whether they participated in the companion study and randomized to the HMP or waitlist control group. Waitlist participants will be informed that they may complete the HMP following study participation, if desired.

HMP group participants will be instructed on downloading and installing a study-specific version of the HMP app. The 4-week meditation program will take approximately 60 minutes to complete each week. The program will be self-paced and completed remotely. While completing the HMP each week, participants will listen to podcast-style lessons in the app to learn about meditation from scientists and experts in well-being. The app will also guide participants through seated and active meditations. Participants may have the option to provide demographic and meditation experience information and complete the Healthy Minds Index questionnaire to assess their current level of well-being within the app. The app will collect activity data (e.g., when, how long, and what content was listened to), device type, and GPS data (if enabled by the participant). Participants will also occasionally answer pre- and post-practice questions. The app will not collect any identifying information. Participants will have the option to continue using the HMP app after completing the 4-week program. If they choose to do so, we will continue to monitor their app usage and any other data collected through the HMP app throughout the study to learn more about its long-term impact on well-being. The HMP app is considered an FDA regulated device that should qualify as a "non-significant risk (NSR) device". We are seeking an NSR determination and have, therefore, uploaded an NSR request letter in ARROW (see Drug and Device Documents section, #2 Device Documentation).

Timepoints 2-5 - During & Post-Intervention Activities: HMP group participants will complete online measures (see section **13.2 Schedule of study procedures**) remotely through REDCap for Timepoints 2-5 during the same weeks as the 4-week intervention. The measures will take 10 to 45 minutes to complete each week. Waitlist participants will also complete most of the same measures over 4 weeks. Participants will have approximately one week to complete each set of self-paced activities.

Timepoint 6 - 3-Month Follow-Up: About three months after Timepoint 5, participants will complete a final set of measures (see section **13.2 Schedule of study procedures**) remotely online through REDCap, which will take 30 to 45 minutes.

13.4 Data collected during the study

Data elements: The following data will be collected directly from participants:

- Behavioral pattern separation task data
- Data collected from the participant's smartphone by the HMP app: activity data (e.g., when, how long, and what content was listened to), device type, GPS data (if enabled by the participant), pre- and post-practice question responses, optional demographic and meditation experience information, and Healthy Minds Index questionnaire responses
- Data collected from the participant's smartphone by the location tracking app ("FollowMee"), such as date, time, GPS location (latitude and longitude coordinates), direction, altitude, and speed of travel, device type, and device ID

Surveys: A subset of the following surveys will be completed by participants during each assessment time point:

- Attention Check Items
- Behavioral Risk Factor Surveillance System (BRFSS) Adverse Childhood Experiences (ACE) Module
- Demographics
- Demographics & Meditation Experience
- Determinants of Meditation Practice Inventory-Revised (DMPI-R)
- Digital Working Alliance Inventory (DWAI)
- Five Facet Mindfulness Questionnaire (FFMQ), Awareness Subscale
- Flourishing Measure
- Global Physical Activity Questionnaire (GPAQ)
- Healthy Minds Index (HMIndex)
- Mainz Inventory of Microstressors (MIMIS)
- Marlowe-Crowne Social Desirability Scale (MCSD)
- Mindfulness-Based Program – Meditation-Related Adverse Effects Scale (MBP-MRAES)
- Mindfulness Adherence Questionnaire (MAQ)
- NIH Toolbox Loneliness
- Pre- & Post-Practice Items
- PROMIS Item Bank - Emotional Distress - Anxiety (Computer Adaptive Version)
- PROMIS Item Bank - Emotional Distress - Depression (Computer Adaptive Version)
- PROMIS Item Bank - Sleep Disturbance (Computer Adaptive Version)
- Perceived Stress Scale (PSS)

- PTSD Checklist (PCL-5)

Source records: All data will be collected directly from participants. No data will be collected from any of the following sources:

- ☐ UW Health medical or billing records via ICTR's Clinical Research Data Service (CRDS)
- ☐ UW Health HealthLink Records (study team will directly access)
- ☐ Data from departmental QA or QI database
- ☐ Data from UW Health Enterprise Data Warehouse (EDW)
- ☐ Data from PACS (Picture Archiving and Communication System); *specify whether study will use the clinical or research instance in the Radiology Department's warehouse*: _____
- ☐ Data from Center for Medicare/Medicaid Services
- ☐ Data from publicly available datasets (e.g., U.S. census data)
- ☐ Data from outside institutions or organizations (specify: _____)
- ☐ Other (specify: _____)

13.5 Long-term follow-up

There are no current plans for long-term follow-up other than Timepoint 6 (3-Month Follow-Up), which is part of the research procedures listed above. For those in the HMP group, we will continue to use any data collected through the HMP app (e.g., usage data) until Timepoint 6. Additional follow-up activities may be planned by study personnel and/or collaborators. The consent form includes a section where participants can opt in to future contact.

14.0 Comparison of usual care and study procedures

14.1 Alternatives

N/A - All procedures are performed solely for research purposes. Individuals may elect to not enroll in this study, as it is completely voluntary.

15.0 Withdrawal of Participants

15.1 Withdrawing participants without their consent

We anticipate that we will withdraw a participant from the study: 1) if we determine that participation in the study is exposing the participant to an unacceptable level of risk, 2) to maintain data integrity (e.g., if a participant is not following study procedures or may be deliberately providing false information), or 3) if the study is stopped by the sponsor or researchers.

15.2 Procedures for orderly termination

When withdrawing a participant, we will: 1) thank the participant for their participation, 2) explain the reason(s) for termination, 3) explain that the participant will be paid for the portion of the study that they completed (as described in the consent form), 4) ask the participant if they

have any questions or comments about the study, and 5) inform the participant that the HMP app is available to use free of charge. We will change the participant status to withdrawn in REDCap; however, we will retain and use data collected prior to withdrawal.

15.3 Procedures for participant-initiated withdrawal

When a participant chooses to withdraw from the research, we will: 1) thank the participant for their participation, 2) determine if the participant will be fully or partially withdrawing (if partial, determine which procedures the participant will be completing), 3) explain that the participant will be paid for the portion of the study that they completed (as described in the consent form), 4) ask the participant their reason for withdrawing (if they choose to provide it), 5) ask the participant if they have any questions or comments about the study, and 6) inform the participant that the HMP app is available to use free of charge. We will remove the withdrawn participant from REDCap; however, we will retain and use data collected prior to withdrawal.

16.0 Data Management and Confidentiality

16.1 Quality control

Study staff will conduct periodic checks throughout data collection to ensure that all data (e.g., survey, behavioral task, HMP app activity, and location tracking) are recorded as expected and to look for any missing and/or aberrant data.

16.2 Steps to secure the data

- ☒ Data will be coded, and the "key" linking identities to codes will be kept separately from the data.
- ☐ Data will be coded, and the "key" linking identities to codes will be kept on paper only. The study data will be stored electronically and labeled only with codes.
- ☒ Only those listed as key personnel will have access to the "key."
- ☐ Access to the "key" will be limited to the following person (e.g., Database Administrator): _____
- ☒ This study is funded by the National Institutes of Health and is covered by a Certificate of Confidentiality.
- ☐ This study is NOT funded by the National Institutes of Health but because it will collect sensitive information, the research team will apply for a Certificate of Confidentiality to protect data from being requested without the subject's consent as part of a legal proceeding.
- ☐ Other: _____

Data collection and storage: Data will be collected, protected, and shared using REDCap, which is administered by ICTR at UW-Madison. This is a web-based data collection program that is HIPAA and IRB compliant, and allows for the safe and secure collection and storage of clinical assessments, questionnaires, and physiological data. Data will also be gathered through the HMP app and through a GPS location tracking app ("FollowMee"). A short pre-screening survey for participants recruited from Prolific will be administered in Qualtrics. We will not collect any identifying information in Qualtrics, and participant responses will only be identified by a

Prolific ID. Location tracking data collected in the FollowMee app will not be associated with any participant information other than a non-identifiable device ID and subject ID. Participant data will be coded with subject ID numbers. All data will be managed by the study PI. Access to the data will be given only to HIPAA and CITI qualified and trained study team members. Data will be kept indefinitely on HIPAA compliant password-protected secure servers.

Confidentiality: We will make every effort to maintain the privacy and confidentiality of participants involved in the study. This includes taking the following steps:

- Staff will participate in initial training, follow-up training, and ongoing monitoring and supervision to ensure understanding of ethical issues involved in this research that includes, but is not limited to, courses offered by UW-Madison's Human Research Protection Program, and a training on HIPAA and measures to protect confidentiality.
- The electronic key that links the participant name with ID number will be kept in a secure electronic database file on REDCap and on the password-protected secure server for the Center for Healthy Minds. It will be accessible only by authorized study staff.
- Any personal identifiers linked to data will be removed and replaced by code numbers in all records.
- The highest security features in REDCap will be enabled for screening questionnaires. Screening data and other questionnaire data collected via REDCap will be downloaded to electronic files that will be kept on the HIPAA compliant secure server for the Center for Healthy Minds. This is the drive on which patient and research subject data that meet the criteria for electronic private health information are stored. We do not store any electronic personal health information (including information gathered as part of the proposed study) locally on any desktop workstations. These files will be password protected and accessible only by the PI and study staff.
- The Qualtrics prescreening survey for participants recruited through Prolific will not collect any identifying information. Participant responses will be identified only by a Prolific ID.
- The HMP app will not collect any identifying information. Information collected on the HMP app will be coded with a subject ID number.
- The FollowMee app will collect minimal data to provide location tracking services (e.g., device ID, device type, date, time, latitude and longitude coordinates, direction, altitude, and speed of travel). No participant information will be associated with these data within the FollowMee app or server other than a non-identifiable device ID and a subject ID. Data will be encrypted while transmitted from participant devices to the FollowMee server and will be deleted from participant devices after transmission. Data will be protected online by an account authentication process. Only authorized study staff will have access to the credentials. FollowMee will store all data on a secure server hosted by Amazon Web Service. Data will be encrypted when downloaded from the FollowMee server, and downloaded data will be saved on the password-protected secure server for the Center for Healthy Minds.
- After location tracking data are downloaded, our staff will protect participant confidentiality by not viewing the minute-by-minute data, other than for the purpose of conducting quality control checks of these data. When reviewing these data, staff will view lists of latitude/longitude coordinates, and will make no effort to link these coordinates to specific places that could reveal embarrassing, stigmatizing, or illicit

information. Data analysis will focus on extracted summary measures across a given day; for example, total distance traveled, number of distinct locations visited, and diversity of locations visited (or "roaming entropy"; see Heller et al., 2020).

- Prior to signing the consent forms for participation in the study, participants will be notified on the consent form that we are included in the list of mandated reporters and that by signing the consent form, they understand that in cases of suspected harm to self or other, the researcher is required by law to report to the appropriate authorities.

16.3 How and where data and/or specimens will be stored and maintained

- ☐ Online Collaborative Research Environment (OnCore) Biospecimen Management
- ☒ Research Electronic Data Capture (REDCap) *Specify which instance you will be using (e.g., ICTR's, Department of Medicine's)*: ICTR's instance of REDCap
- ☐ Other software option that will be stored on departmental server. *Specify the department*: _____
- ☒ Locked filing cabinet or drawer inside a locked room. Specify the building: Center for Healthy Minds
- ☒ Other (describe): Data will be temporarily stored on the secure servers for the HMP app and FollowMee app until they are transferred to the password-protected secure servers for the Center for Healthy Minds.
- ☐ Data will not be stored or accessed on portable devices.
- ☒ Portable devices will be used to access secure web-based data collection sites such as ICTR's REDCap and to access the HMP app. The FollowMee app will passively collect location data from participant's smartphones. No data will be stored locally on the device.
- ☒ Data stored on portable devices will be coded with the key stored separately. No identifiers will be stored on portable devices.
- ☐ Data stored on portable devices and therefore only encrypted devices will be used.

16.4 Management of identifiers

- ☐ Identifiers will be destroyed after all data has been collected.
- ☐ Identifiers will be destroyed at study closure.
- ☐ Identifiers will be destroyed at study closure or at the time of publication.
- ☒ Identifiers will be kept indefinitely so that we can contact participants who consented to future contact. All data will be labeled with a participant ID code. The key linking participant name with participant ID code will be stored in ICTR's instance of REDCap and on a password-protected secure server with access limited to authorized study staff.

16.5 Data/specimen handling for multi-site research

N/A - This study is not multi-site.

16.6 Data sharing

We may share coded data (e.g., questionnaire, behavioral task, location) with researchers within or outside of UW-Madison to address future research questions not included in this application,

with a complementary study being conducted at the Center for Healthy Minds (i.e., the "BeWell Study"; PI: Richard Davidson; Protocol: 2021-0991) which is utilizing many of the same survey and behavioral task measures, and/or with journals where open data sharing policies are encouraged or are a requirement for publication (e.g., PLoS ONE). Coded data may be shared as Supplemental Information uploaded to journal websites and/or shared on a UW data sharing website such as "Minds@UW" (http://researchdata.wisc.edu/data-access-2/) or UW-Madison Box (https://uwmadison.box.com). UW-Madison Box will only be used to transfer coded data and will not be used for long-term data storage. Data will be directly uploaded to the journal website or the data sharing website. Confidentiality will be protected by coding the data with new subject numbers. The code linking the new subject numbers to the original subject numbers will be kept on our secure server and will be maintained by study staff.

We may share fully de-identified data from the study on data sharing platforms (e.g., OpenNeuro, NIMH Data Archive) for use by non-collaborators. Data shared on data sharing platforms will be uploaded via the internet. Confidentiality will be protected by stripping the data of all identifiers, including HIPAA identifiers.

We may follow-up with participants from this study in future research studies. We will ask participants on the consent form if they would like to be contacted about future studies. If they agree, their contact information (e.g., name, phone number, email address, home address) will be kept on the Center for Healthy Minds' secure server indefinitely. Only authorized study staff will have access to this information. The participant's contact information will not be stored with their data. Future studies may include analysis of the information from this study alone or in combination with data collected in other studies. Any future research utilizing these data will be submitted as a separate application to the IRB prior to their use, if required by IRB policies and/or guidance.

17.0 Provisions to Protect the Privacy Interests of Participants

17.1 Steps to protect privacy interests

- ☒ Procedures will be performed in a private area where others cannot see the procedures being performed or overhear the conversation between subjects and researchers.
- ☒ All members of the study team are up to date on their institutional HIPAA training.
- ☐ The study is not collecting information that could pose legal or reputational risks to participants.

All study procedures will be completed remotely in a setting of the participant's choice. We will recommend that participants complete remote study procedures in a private room.

17.2 Justification for sensitive information

The study screener will ask questions about current and/or past symptoms of various mental illnesses. The study surveys include questions related to negative childhood experiences, depression, anxiety, and stress. One aim of the study is to investigate whether the meditation training intervention reduces perceived stress, which is related to depression and anxiety. Current

or past history of various psychiatric disorders may confound aims of the study and thus are part of the exclusionary criteria.

17.3 Steps to make participants feel at ease

The study description, consent form, and introduction to the surveys/interview will all include language stating that 1) participation is voluntary, 2) some questions may be of a sensitive nature, and 3) participants may skip any items that they are not comfortable answering, except for certain required items (e.g., the PSS is required because it is a primary study measure). We will provide participants with a description of the procedures that will be performed during study visits and will ask participants if they are comfortable proceeding. We will let participants know that they can ask questions or tell us concerns at any time and we would be happy to help.

18.0 Sharing of Results

18.1 Whether results will be shared with participants or others

All measures (surveys, behavioral task, & location) are for research purposes only and individual results may not be meaningful. We will not share individual results with participants or report results in participant health records.

18.2 Plans to share study results with the public

We will share study results with the public via manuscripts and/or open source databases. The Center for Healthy Minds website and/or other social media platforms may share information about study results and/or publications.

19.0 Data and Specimen Banking

19.1 Description of data and specimen banking

We may bank any data collected during this study (e.g., questionnaire, behavioral task, location) for future use to address research questions not included in this protocol. Banking of data will not be optional. Banked data will be stored indefinitely on ICTR's instance of REDCap and on a password-protected secure server with access limited to authorized study staff.

19.2 Information associated with banked data and specimens

Study data will be coded with the participant ID. The code linking data to identifying information will be kept on a password-protected secure server and ICTR's instance of REDCap with access limited to authorized study staff.

19.3 Procedures to release banked data and specimens

There are no limits on future use of banked data. Any future research utilizing these data will be submitted as a separate application to the IRB prior to their use, if required by IRB policies and/or guidance. Other researchers inside and outside of UW-Madison may request banked data from the Principal Investigator.

19.4 Withdrawing banked data or specimens

Participants may withdraw their banked data from future research use. If we receive a withdrawal request from a participant, we will destroy all of their banked data.

20.0 Study Analysis

20.1 Statistical hypotheses

H1: HMP vs. waitlist participants will show (a) lower scores on the perceived stress scale, (b) improved performance on the pattern separation task, and (c) increased "experiential diversity" measured using GPS location tracking.

H2: Within the HMP group, greater decreases in perceived stress will be correlated with improvements/increases in outcomes b-c.

20.2 Sample size justification

We plan to enroll 150 participants, assigning two-thirds to the HMP group and one-third to the waitlist control group, and anticipate 10% dropout. This sample size affords us 80% power to detect medium effect sizes ($d = 0.5$) for our primary outcome of perceived stress at $p < 0.05$. A recent study of the Healthy Minds Program vs. waitlist control (Hirshberg et al., 2021) identified a similar effect size for a composite "distress" measure, which was an aggregate of perceived stress and PROMIS anxiety/depression scores, and another previous study suggested a SD of 0.5 reflects a minimal clinically important differences for the Perceived Stress Scale (Platinga et al., 2017). For correlation analyses, we have 80% power to detect medium-to-large correlations ($r = 0.41$) at $p < 0.0125$ (0.05/4 outcomes).

20.3 Participant population(s) for analysis

Participants will be assigned to HMP and waitlist groups at a 2:1 ratio.

20.4 Statistical methods

Group differences for the intervention will utilize linear mixed effects models with a random intercept and slope for each participant to account for non-independence of error and to maximize use of data with missing observations. We will conduct Pearson correlation analyses using difference scores between baseline and post-intervention/follow-up timepoints to test whether reductions in perceived stress are associated with behavioral or imaging outcomes hypothesized to contribute to differences in perceived stress.

20.5 Planned interim analysis

Given the low risk of the intervention, no interim efficacy or safety analyses are planned.

20.6 Handling of missing data

Linear mixed effects analyses account for missing data in a robust manner relative to, e.g., ANOVA. We will use all available observations and do not plan to impute missing data. We will document reasons for missing data, evaluate whether data appear missing at random, and evaluate the impact of missing data using sensitivity analyses based on the nature of missing data.

21.0 Potential Benefits to Participants

21.1 Potential benefits
Participants may benefit from using the HMP, which is designed to introduce meditation practice as a way of reducing stress and developing greater balance, ease, and fuller participation in life. This meditation training is a way of learning to relate directly to whatever is happening in your life including the challenges of stress, pain, illness, and everyday demands. Waitlist control participants can use the HMP after completion of the study at no cost.

21.2 Direct benefits
There are no direct benefits for participants.

22.0 Risks to Participants

22.1 Risks, discomforts, hazards, or inconveniences
Risk of emotional responses:
Study surveys include questions about mental health that could affect a participant's mood or make them feel embarrassed. Emotional upset due to study participation is a potential but unlikely risk. In our experience from previous studies, it is rare for a participant to find self-report questionnaires to be extremely upsetting.

Risk of location tracking:
GPS location data collected from participants' smartphones could be used to see specific locations that participants have visited and whether participants may have engaged in activities or visited places that are potentially stigmatizing or embarrassing.

Risk of confidentiality breach:
There is a slight risk of breach of confidentiality, which could result in legal implications or stigmatization. There is a chance that concerns about safety (e.g., self harm, possible child abuse) will be discovered during the course of the study, and that these discoveries could require mandatory reporting and place subjects at possible legal risk. There is the risk that information, such as health information or GPS location information, could become known to subjects, doctors, or others. If this happens it may lead to loss of insurance, difficulty obtaining insurance, an increase in premiums, job loss, reduced employability, and harmful psychological effects on the subject.

22.2 Risks associated with delaying standard treatment
N/A

22.3 Procedures that have unforeseeable risks
N/A

22.4 Procedures that have potential risks to an embryo or fetus
N/A

22.5 Risks to others who are not participants
N/A

22.6 Minimizing risks
Minimizing risk of emotional responses:
We will inform participants in the consent form and in survey instructions that some questions may ask about sensitive topics and that they may skip any items that they are not comfortable answering, except for certain required items (e.g., the PSS is required because it is a primary study measure). As stated in the consent form, participants are free to discontinue at any point during the experiment.

If a participant reveals suicidal ideation, self-harm, or intent to harm others, study staff will consult with clinical research personnel. A clinician will contact the participant by phone to assess intent, the level of risk, and provide referrals as needed. In the circumstance that an individual indicates that self-harm or harm to others is imminent, 911 will be called. All interactions regarding suicide risk and referral will be carefully documented and closely tracked by the clinical research personnel. A formal incident report will be filed with the IRB in cases in which a clinician notifies authorities. All participants will be provided with therapeutic resources regardless of their responses.

Minimizing risk of location tracking:
We will inform participants in the consent form about how we will use and protect location data. The FollowMee app will not collect any identifying information. Location data will only be associated with a non-identifiable device ID and subject ID. Data will be stored on secure password-protected servers. Study staff will not view real-time GPS locations, other than to confirm that the FollowMee app is functioning correctly. Data will be encrypted during download, and security measures for the Center for Healthy Minds network will provide protection against data breach. After the data are downloaded, our staff will protect participant confidentiality by not viewing or analyzing the minute-by-minute data, other than for the purpose of conducting quality control checks of these data. When reviewing these data, staff will view lists of latitude/longitude coordinates, and will make no effort to link these coordinates to specific places that could reveal embarrassing, stigmatizing, or illicit information. Data analysis will focus on extracted summary measures across a given day; for example, total distance traveled, number of distinct locations visited, and diversity of locations visited (or "roaming entropy"; see Heller et al., 2020).

Minimizing risk of confidentiality breach:
We will use data storage procedures to reduce the risk of confidentiality breach (e.g., data coding, secure storage, trained personnel). Additionally, although GPS location information will be collected within the GPS application, this application will not have access to any identifiable participant information or other data (e.g., questionnaire responses). This will be made explicitly clear to the participants. Because potential safety concerns (e.g., self harm, possible child abuse) may require mandatory reporting and place subjects at possible legal risk, we will inform participants about this limit to confidentiality in the consent form. Also, this study is funded by

the NIH and has a Certificate of Confidentiality that provides additional confidentiality protections.

23.0 Provisions to Monitor the Data to Ensure the Safety of Participants

23.1 Data and safety monitoring plan

Adverse events will be tracked (including details of the incident, actions taken, and follow-up steps) by study staff and reported to the PI. The PI will be responsible for the monitoring and reporting of adverse events, as necessary, to the IRB.

Other notable incidents that occur during recruitment, consent, or data collection that are determined to be unexpected and related to the study procedures will be reported in a detailed log on an annual basis (at the time of continuing review). The PI will be responsible for informing the IRB immediately of any life threatening incidents as well as take appropriate action to stop the study, release a participant from the study, or modify procedures to reduce and/or eliminate the occurrence of the risks.

The PI will review information on adverse events, protocol deviations, data quality, participant recruitment, accrual, and retention (including reasons for dropout), whether all participants met inclusion criteria, and demographics. This information will be provided in biannual reports to an Independent Monitor who will make recommendations regarding the safe continuation of the study and whether any changes to the protocol are needed to ensure participant safety. Once annually the Independent Monitor will forward an approved report to the UW Health Sciences IRB and NIMH.

Given the safety and risk level of the intervention and study procedures, we cannot anticipate any conditions that would trigger an immediate suspension of the research.

24.0 Economic Burden to Participants

24.1 Potential costs

Since data collection will be done remotely, there are few potential costs associated with participation.

25.0 Resources Available

• **Will the research be conducted outside School of Medicine and Public Health or UW Hospitals and Clinics (e.g. the researcher does not have an SMPH research feasibility attestation for this study)?**	☒ YES (complete 25.1) ☐ NO (remove text below, but retain this section)

25.1 Resources available to conduct the research

The Center for Healthy Minds has ample experience running large-scale, longitudinal studies. As most studies have moved to remote data collection in the past year (IRB protocols: 2020-0533, 2020-1454, and 2019-0893), we have been successful at recruiting a large number of participants with high retention rates.

Data collection for this study will be completed remotely over approximately 3 years.

We will inform participants that they should contact their healthcare provider if any concerns arise when answering survey questions. A therapeutic resource list will be provided to all participants upon completion of the study.

Study staff will meet on a regular basis to discuss study design, implementation, processing, and analyses. We will discuss task assignments and study updates at these meetings.

26.0 Multi-Site Research

N/A

27.0 References

Heller AS, Shi TC, Ezie CEC, Reneau TR, Gibbons C, Baez LM, Hartley CA (2020). Association between real-world experiential diversity and positive affect relates to hippocampal-striatal functional connectivity. Nature Neuroscience. 3(7):800-804. doi: 10.1038/s41593-020-0636-4.

28.0 Appendices

N/A