# Mechanisms of Mindfulness-based Interventions

**David R. Vago Ph.D. (PI, Director of CNIM Lab)**
Poppy L.A. Schoenberg, Ph.D. (PI)
Resh Gupta, M.S. (PI)

Vanderbilt University Medical Center
Osher Center for Integrative Medicine
Department of Physical Medicine & Rehabilitation
Chair: D.J. Kennedy, M.D.

ClinicalTrials.gov Identifier: NCT03571386

Institutional Review Board
Informed Consent Document for Research

**Key Study Personnel**

Landrew Sevel, Ph.D.
Michelle Foote-Pearce, MSN

**Table of Contents:**

## 1.0 Background

**ABSTRACT**
The state of mindfulness can be described as a form of meta-awareness in which attention is allocated to the present moment of external and internal sensory or mental experience, without reactivity, and without dwelling on any particular sensory or mental object with judgement or evaluation. Mindfulness-based Interventions (MBIs) are a family of standardized cognitive and behavioral therapies that focus on cultivating mindfulness-related skills for improving maladaptive cognitive, emotional, and behavioral processes.

This mixed methods pilot study proposes to investigate proposed neurobiological, physiological, psycho-social-behavioral, and cognitive mechanisms by which MBIs may improve health outcomes. Target (mechanism) engagement is expected to facilitate identification of individuals who are most likely to benefit (or not) from MBIs and further develop targeted interventions for optimization of delivery. Although there are very specific aims and hypotheses to be tested, this preliminary exploratory investigation will provide feasibility data and allow for refining existing hypotheses for larger research proposals to be submitted for extramural grant support.

**BACKGROUND & RATIONALE**
On closer analysis, mindfulness has been more clearly operationalized as "the continuous discriminative attentional capacity for encoding and recollecting experiences efficiently—without forgetfulness or distraction, and in the appropriate context". From a cognitive perspective, it can be conceptualized as a state of meta-awareness in which attention is allocated to the present moment of external and internal sensory or mental experience, without reactivity, and without dwelling on any particular sensory or mental object with judgment or evaluation. Through cultivation of this state of meta-awareness, it is believed that multiple other skills are developed. These skills have been described as six fundamental mechanisms by which mindfulness functions (Vago and Silbersweig 2012):

- **1) Intention & Motivation**
  - Effortful to Effortless
  - Self-focused to Other-focused
- **2) Attention Regulation**
  - Sustained Attention, control, & flexibility (engagement, disengagement),
  - Meta-awareness (de-centering & executive monitoring)
- **3) Emotion Regulation**
  - Equanimity,
  - Inhibitory control
- **4) Extinction and Reconsolidation**
  - Mental habits & biases shifted toward adaptive trajectories
- **5) Prosociality**
  - Empathy, Theory of Mind, & Altruistic Behavior
- **6) Sensory Clarity**
  - Embodied cognition

Despite successful medication and psychotherapies, stress-related health problems, pain outcomes, and psychopathologies rarely respond completely and are not always cost-effective. MBI's offer a low-cost, non-pharmacological alternative with a growing evidence-base.

A major challenge in improving treatment response and overall outcome in patients with high levels of stress or psychopathology, who are well characterized with mild to moderate severity, and whose residual symptoms are not addressed with a potentially effective medication for an adequate length of time lies within

- **(1) identifying and testing the neurobiological, behavioral, and psycho-social mechanisms by which symptom reduction occurs and**
- **(2) identifying and testing a particular clinical endophenotype of individuals who may (or may not) benefit from augmentation through a mindfulness-based intervention**

**Mindfulness-based Interventions (MBIs)**

Mindfulness-based Stress Reduction (MBSR). (see Appendix A) Mindfulness-Based Stress Reduction (MBSR) is a well-defined and systematic patient-centered educational approach which uses relatively intensive training in mindfulness meditation as the core of a program to teach people how to take better care of themselves and live healthier and more adaptive lives. The prototype program was developed at the Stress Reduction Clinic at the University of Massachusetts Medical Center. This model has been successfully utilized with appropriate modifications in a number of other medical centers, as well as in non-medical settings such as schools, prisons, athletic training programs, professional programs, and the workplace.

We emphasize that there are many different ways to structure and deliver mindfulness-based stress reduction programs. 8-week MBSR treatment protocol(Kabat-Zinn 1982) is standardized and incorporates mindfulness skills into meditation training and self-inquiry to assist people with stress, pain and a range of conditions and life issues that were initially difficult to treat in a hospital setting. The group intervention entails weekly group meetings (two-hour classes) and a one-day retreat (six-hour mindfulness practice) between sessions six and seven, homework (45 minutes daily), and instruction in three formal techniques: mindfulness meditation, body scanning and simple yoga postures.

a) Group Pre-program Orientation Sessions (2.5 hours) followed by a brief individual interview (5-10 minutes)
b) Eight-weekly classes 2.5-3.5 hours in duration
c) An all-day silent retreat during the sixth week of the program (7.5 hrs)
d) "Formal" Mindfulness Meditation Methods:

- Body Scan Meditation - a supine meditation
- Gentle Hatha Yoga - practiced with mindful awareness of the body
- Sitting Meditation - mindfulness of breath, body, feelings, thoughts, emotions, and choiceless awareness
- Walking Meditation

e) "Informal" Mindfulness Meditation Practices (mindfulness in everyday life):

- Awareness of pleasant and unpleasant even
- Awareness of breathing

- Deliberate awareness of routine activities and events such as: eating, weather, driving, walking, awareness of interpersonal communications

f) Daily home assignments including a minimum of 45 minutes per day of formal mindfulness practice and 5-15 minutes of informal practice, 6 days per week for the entire duration of the course
g) Individual and group dialogue and inquiry oriented around weekly home assignments including an exploration of hindrances to mindfulness and development and integration of mindfulness-based self-regulatory skills and capacities
h) Incorporation of exit assessment instruments and participant self-evaluation in Class 8

• Total in-class contact: 30+ hours
• Total home assignments: minimum of 42-48 hours
• Total group Orientation Session time: 2.5 hours

Mindfulness-based Cognitive Therapy (MBCT) (Appendix B). 8-week MBCT treatment protocol is standard as defined by Segal, Williams and Teasdale(Segal, Williams et al. 2013) with some minor modifications to address suicidality and presence of acute symptoms, i.e., introduction of crisis plans and cognitive components addressing suicidal cognitions and hopelessness. MBCT uses core meditation techniques (i.e., focused attention, open monitoring, body scan, breathing space, yoga) with a focus on mindful awareness as its core therapeutic ingredient and adds components of cognitive behavior therapy (CBT) (Segal, Williams et al. 2013).

**8 x 120-minute weekly sessions**

SESSION 1: AWARENESS & AUTOMATIC PILOT
SESSION 2: DEALING WITH BARRIERS & LIVING IN OUR HEADS
SESSION 3: GATHERING THE SCATTERED MIND
SESSION 4: RECOGNIZING AVERSION & STAYING PRESENT
SESSION 5: ALLOWING/LETTING BE
SESSION 6: THOUGHTS ARE NOT FACTS
SESSION 7: HOW CAN I BEST TAKE CARE OF MYSELF?
SESSION 8: USING WHAT HAS BEEN LEARNED TO DEAL WITH FUTURE MOODS

## 2.0 Specific Aims

Pre-Study Paradigm Testing: Before commencing the research delineated in this protocol, we will collect EEG and fMRI data from 30 healthy subjects between the ages of 18 and 55. This will allow us to test all of our experimental paradigms and make sure they are working properly prior to recruiting the patients for the research described in this protocol.

We propose to test candidate neurophysiological, behavioral, and psychosocial mechanisms by which MBIs improves outcomes in patients with high levels of 1) reported stress; 2) chronic pain; 3) clinical anxiety; 4) clinical depression with persistent residual symptoms. Specifically, we aim to:

(1) Use fMRI to test whether fronto-limbic neural activation patterns mediating IC in the context of emotion are modulated by MBIs.

(2) **Aim 2: To examine the neurobiological markers of psychopathology, by investigating the neurophysiological substrates (EEG/ERPs) of working memory and executive function in depressed and anxious patients.**

a. (tested by the N-Back task). Lastly, post-MBCT or MBSR will facilitate improved cognitive processing with an emotional memory manipulation, i.e. high cognitive load, mood-incongruous (happy/positive) facial stimuli, indexed by increased amplitudes of N170, VPP, and P300 ERPs during relevant stimuli trials.

(3) **Aim 3: To determine whether an 8-week MBCT modifies P1 threat-related attentional bias markers in anxious patients.**

(4) **Aim 4: To investigate the relationship between P1 threat-related attentional bias markers, acute treatment response and durability in anxious patients enrolled in MBCT.**

(5) **Aim 5. Assess the role of sustained attention (i.e. vigilance) and inhibitory control as self-regulatory mechanisms predicting improvements on patient-reported outcomes for patients with high stress**

(6) **Aim 6. Assess effects of treatment type and the interaction with self-regulatory measures on clinical outcomes**.

### 3.0 Inclusion/Exclusion Criteria

Eligibility Criteria for Pre-Study Paradigm Testing:

- Before commencing the research delineated in this protocol, we will collect EEG and fMRI data from 30 healthy subjects to test all of our experimental paradigms and make sure they are working properly.
- Flyers and ResearchMatch will be used to circulate information about the study to the Vanderbilt campus and surrounding community.
- The subjects must be between the ages of 18 and 55.
- The 30 subjects will not complete the full pre-screening questionnaire, but will receive a phone screen to make sure they can safely participate in the EEG and fMRI protocol.

Eligibility Criteria Across All Study Arms:

- At prescreen, must be currently registered for MBCT or MBSR; at posttest, must have attended five of eight sessions for “completion”.
- Must possess English language skills sufficient for providing informed consent, completing questionnaires, and understanding instructions
- Age range: 18-55

- If currently taking maintenance anti-depressant and/or anti-anxiety medication, must have a "stable" regimen as indexed by no medication or dosage changes within the past month
- No prior diagnosis of bipolar I, bipolar II, psychotic personality disorder, borderline personality disorder, and/or narcissistic personality disorder
- No current history (≤ 6 months) of substance abuse/dependence
- No current history (≤ 6 months) of regular meditation practice (>1 session/week; >10 min/session)
- No history of medical illness associated with possible changes in cerebral tissue or cerebrovasculature (e.g., stroke) or with neurologic abnormality (e.g., seizure disorder, cerebrovascular or neoplastic lesion, neurodegenerative disorder, or significant head trauma, defined by loss of consciousness of ≥ 5 minutes)
- No current suicidal ideation

*Depression Arm (consists of fMRI scan, EEG with behavior, and self-report measures at pre- and post-treatment testing)*

- Beck Depression Inventory-II (BDI-II) score ≥ 14 (an indicator of depressive symptoms of mild to high severity)
- No fMRI contraindications: pregnancy, claustrophobia, or presence of a ferromagnetic object, including orthodontic braces

*Anxiety Arm (consists of EEG with behavior, fMRI scan, self-report measures at pretest and posttest)*

- Diagnosed (via SCID-V Screener) with an anxiety disorder (i.e., generalized anxiety disorder, panic disorder, specific phobia)
- Score of ≥40 on the Trait subscale of the Spielberger State-Trait Anxiety Inventory (an indicator of anxious symptoms of moderate to high severity)

*Stress Arm*

- Moderate to high stress is necessary for inclusion on behavioral testing/self-report
- Scores on PSS pre-screen > 14 would be considered moderate to high perceived stress.

*Blood Draws (consists of a 10-mL draw at pre-treatment baseline and post-treatment testing; optional for depression/anxiety arm participants)*

Eligibility Criteria:

- At least 110 pounds
- Generally healthy by self-report on day of collection (i.e., free of cold and flu symptoms on the day of collection, no infections within two weeks prior to collection, no known sickle cell disease)
- Including the study draw, blood donation for clinical or research purposes within the preceding eight weeks will not exceed 550 mL
- No more than one blood draw will have occurred during the preceding week

*fMRI and EEG exclusion criteria*

- history of sustained loss of consciousness, major neurological or medical illness (including significant head trauma defined by loss of consciousness *≥5-minutes duration)*, alcoholism or other substance abuse, significant learning disability, left-handedness, pregnancy,
- fMRI specific: claustrophobia, presence of a ferromagnetic object, presence of opiates and/or amphetamines through urine tests on day of scans.

## 4.0 Enrollment/Randomization

Pre-screening questionnaire using REDCap will be assessing eligibility criteria for the multiple diagnostic arms and methodologies in this study. Suicidal ideation is probed in the BDI-II (item 9) administered in the pre-screening questionnaire and in weekly assessments. Endorsement of any response other than a 0 (indicative of no suicidal ideation) will automatically prompt an email alert to the PI, the study coordinator, Edith Cloyd, JD, MSN, PMHNP-BC (psychiatric nurse practitioner who has 12+ years of experience diagnosing and treating people with a wide range of psychiatric disorders, including depression), and Landrew Sevel, Ph.D., clinical psychologist at the Osher Center. Follow-up to assess risk and clarify an action plan for protecting the participant will occur within 24 hours and is detailed in the attached suicide safety plan.

## 5.0 Study Procedures

**BEHAVIORAL OBSERVATION**

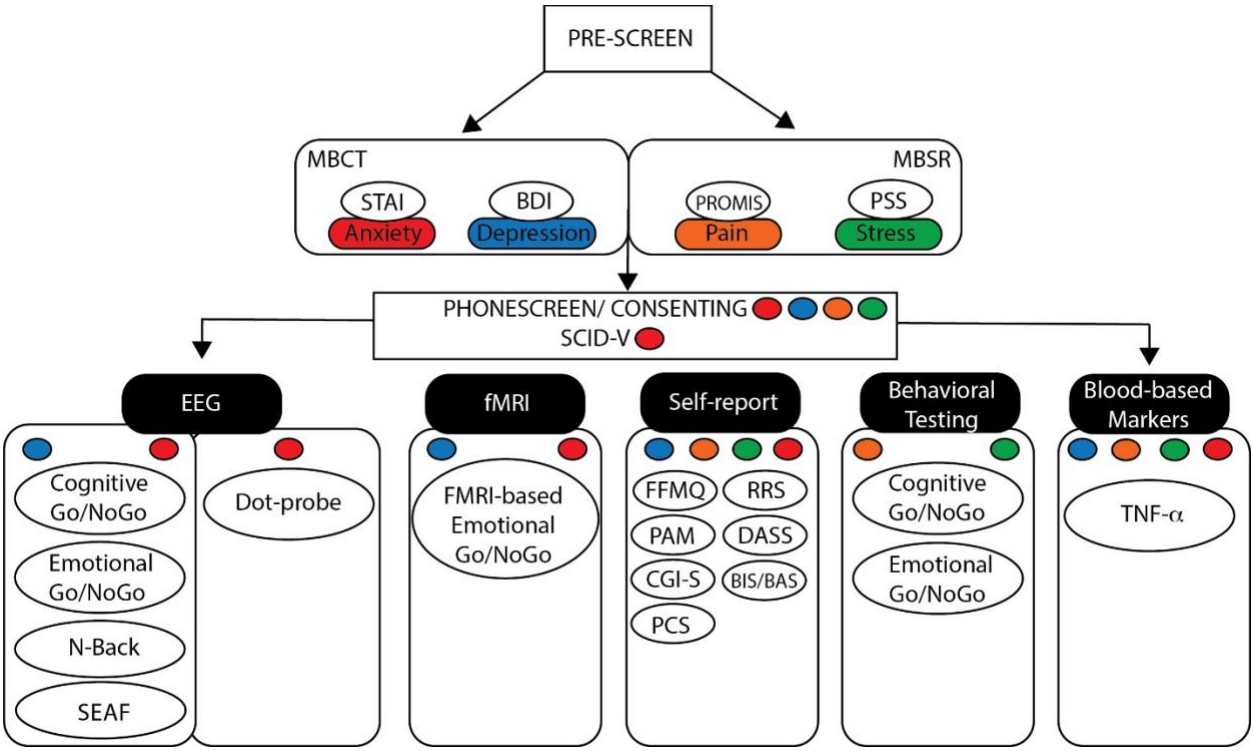
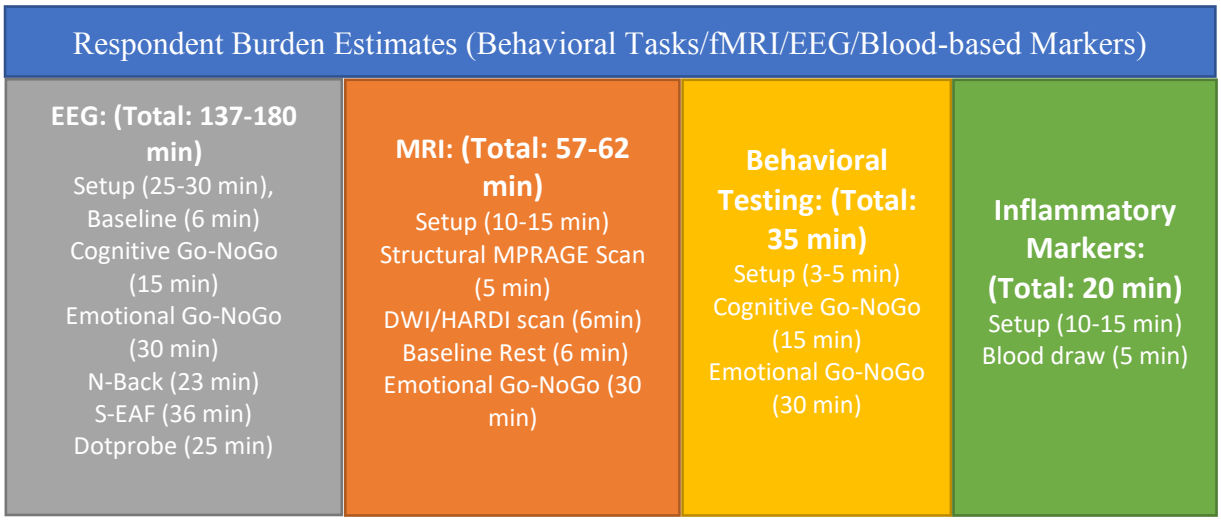



FIGURE 1. Inclusion criteria and allocation of research protocol. Pre-screening includes demographics and surveys specific for determining extent of anxiety (STAI), depression (BDI), and stress (PSS). Subjects with moderate levels of depression or anxiety will then have the choice to participate in EEG (cognitive go-nogo, emotional go-nogo, n-back, , and S-EAF tasks) and fMRI (fMRI-based emotional go-nogo task).

Anxious subjects will be recruited specifically for a dot-probe task with EEG protocol. Subjects who are interested in MBSR, have pain and report moderate levels of stress will take part in behavioral testing (emotional go-nogo). All subjects will have the opportunity to provide blood for inflammatory analyses. High anxiety and depression are anticipated to be reported by subjects enrolled in MBCT; whereas, high levels of pain and stress are anticipated to be reported by subjects enrolled in MBSR. RED color indicates symptoms of anxiety from screening, BLUE indicates depressive symptoms; ORANGE indicates pain symptoms; GREEN indicates Stress-related symptoms.




**Self-Report Measures (Pre/post-testing and follow-up)**

**Patient Reported Outcomes Measurement Information System (PROMIS-29)** ®: A flexible set of tools designed to measure self - reported physical, mental and social health and wellbeing across seven PROMIS domains in 29 items: depression; anxiety; physical function; pain interference; fatigue; sleep disturbance; and ability to participate in social roles and activities. The seven domains cover the most relevant areas of self - reported health for the greatest majority of people with chronic illness. **Only the anxiety and pain interference domains will be** with each domain consisting of 4 questions ranked on a 5-point Likert Scale. There is also one 11-point rating scale for pain intensity. Response scores from the items that were answered (not including any screening question). Multiply this sum by the total number of items in the short form. Finally, divide by the number of items that were answered. For example, if a respondent answered 5 of 8 questions and answered all items with the second lowest response option (2), you would sum all responses (10), multiply by the number of items in the short form (8) and divide by the number of items that were answered (5). Here (10x8)/5=16. If the result is a fraction, round up to the nearest whole number. This is a pro-rated raw score which is then converted to a T-score. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10.

**Five Facet Mindfulness Questionnaire (FFMQ; Baer et al., 2006) (7-10 min):** A 39-item assessment of trait mindfulness (encompassing observing, describing, acting with awareness, non-judging, and non-reactivity), which takes roughly 7-10 minutes to complete.

**Rumination Response Scale (RRS; Nolen-Hoeksema & Morrow, 1991) (5-10 min):** 22-item assessment that reliably assesses rumination and not confounded by depression. The 22 items of the RRS measure two aspects of rumination, brooding and reflective pondering. Items are rated on a four-point scale: 1-Almost Never, 2-Sometimes, 3-Often, 4-Almost always. The questionnaire provides scores for the following scales: Brooding, Reflection, and Depression.

**Behavioral Inhibition (BIS/BAS scale; (Carver and White 1994) (10 min):** The BIS/BAS Scale is a 24-item self-report questionnaire designed to measure two motivational systems: the behavioral inhibition system (BIS), which corresponds to motivation to avoid aversive outcomes, and the behavioral activation system (BAS), which corresponds to motivation to approach goal-oriented outcomes. Participants respond to each item using a 4-point Likert scale: 1 (very true for me), 2 (somewhat true for me), 3 (somewhat false for me), and 4 (very false for me). The scale has four subscales that were derived via factor analysis. One subscale corresponds to the BIS. Seven items contribute to this score (e.g., "Criticism or scolding hurts me quite a bit"). The remaining three subscales correspond to three components of BAS. BAS Drive measures the motivation to follow one's goals. Four items contribute to this score (e.g., "When I want something I usually go all-out to get it"). BAS Reward Responsiveness measures the sensitivity to pleasant reinforcers in the environment. Four items contribute to this score (e.g., "It would excite me to win a contest"). BAS Fun Seeking measures the motivation to find novel rewards spontaneously. Five items contribute to this score (e.g., "I crave excitement and new sensations").

**Depression Anxiety Stress Scale (DASS)**[19] (10 min): The Depression, Anxiety and Stress Scale - 21 Items (DASS-21[60,6]) is a set of three self-report scales designed to measure the emotional states of depression, anxiety, and stress. Each of the three DASS-21 scales contains 7 items, divided into subscales with similar content. The depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest / involvement, anhedonia and inertia. The anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. The stress scale is sensitive to levels of chronic non-specific arousal. It assesses difficulty relaxing, nervous arousal, and being easily upset / agitated, irritable / over-reactive and impatient. Scores for depression, anxiety and stress are calculated by summing the scores for the relevant items. The DASS may hold more promise for distinguishing between anxiety and depression, as well as between symptoms of physical arousal and symptoms of generalized anxiety (e.g., tension or agitation)[60]. The DASS-A will be used as the primary outcome measure of anxiety.

**Carol Ryff scales of psychological well-being (Ryff)** (10 min): Two 9-item scale for purpose in life and self-acceptance are included for testing well-being. Participants respond using a six-point format: strongly disagree (1), moderately disagree (2), slightly disagree (3), slightly agree (4), moderately agree (5), strongly agree (6). Responses to negatively scored items (-) are reversed in the final scoring procedures so that high scores indicate high self-ratings on the dimension assessed. Please note, there are no specific scores or cut-points for defining high or low well-being. Those distinctions are best derived from distributional information from the data collected. For example, high well-being (for short or long versions of the scales) could be defined as scores that are in the top 25% (quartile) of the distribution, whereas low well-being could be defined as scores that are in the bottom 25% (quartile) of the distribution.

**Patient Activation Measure Short Form (PAM-13; Hibbard, Mahoney, Stockard, & Tusler, 2005)** (10 min)**:** The Patient Activation Measure is a 13-item scale designed to measure patients' beliefs, confidence, knowledge, and skills regarding health management. Items are rated on a four-point scale with an additional "not applicable" option: (1) Disagree Strongly, (2) Disagree, (3) Agree, (4) Agree Strongly.

**Pain Catastrophizing Scale (PCS; Sullivan, Bishop, Pivik, & Bitcher, 1995)** (5 min)**:** The Pain Catastrophizing Scale is a 13-item scale designed to measure pain on three subscales: rumination, magnification, and helplessness. Items are rated on a five-point scale ranging from (0) Not at all to (4) All the time. A total

PCS score is derived by summing all 13 items. Scores range from 0 to 52, with higher scores indicating greater catastrophizing.

**Daily Survey**

Home Meditation Practice [daily during intervention]: Participants will be asked to record the frequency and duration of formal home practice sessions, which will take roughly 1-2 minutes to complete daily for eight weeks.

**Weekly Survey**

Treatment Regimen Check-In [weekly during intervention, posttest visit]: Participants will be asked to report whether their depression and/or anxiety medication regimen has changed or if any new, additional treatments have been initiated within the past week, which will take roughly 1-3 minutes to complete once weekly for eight weeks.

**Beck Depression Inventory-II** (BDI-II; Beck et al., 1996) [initial screening, weekly during intervention, posttest visit]: A 21-item measure that evaluates key affective, cognitive, and neurovegetative symptoms of depression listed in the *Diagnostic and Statistical Manual of Mental Disorders— Fourth Edition* (*DSM–IV*; American Psychiatric Association, 1994) and takes roughly 5-10 minutes to complete.

**Spielberger State-Trait Anxiety Inventory** (STAI; Spielberger et al., 1983) [initial screening, weekly during intervention, posttest visit]: A 40-item inventory that measures presence and severity of current anxious symptoms (i.e., state anxiety) and a general propensity to be anxious (i.e., trait anxiety). It takes roughly 5-10 minutes to complete.

## 6.0 Risks

There are no immediate or direct benefits to those participating in this study. Clinical symptoms may be reduced through MBCT or MBSR. It is felt that the benefit of the knowledge to be gained outweighs the potential minimal risks noted below.

More specifically, we anticipate that this work will enhance our understanding of the mechanisms by which MBCT and MBSR function to reduce symptoms in a subset of depressed and anxious patients. This study will also contribute important information concerning optimization strategies for individualized treatment of depression and anxiety. Physical risk to participants is minimal. With plans to restrict access to the data as described above, other risks appear small (although impossible to quantify accurately), and potential societal benefits (in increased medical knowledge) large, including new diagnostic strategies, avenues of treatment, and perhaps prevention. The risk-benefit ratio is thus quite favorable.

**Activity:** Researchers will draw a total of 20 mL of blood per participant through venipuncture over the course of this study.
**Risk(s):** Minor pain, redness, soreness, bruising, or infection at the needle stick site; rarely, some people faint
**Risk Minimization:** Prior to drawing blood, participants will be screened in accordance with best practices set forth by the American Red Cross (as noted previously in the Specimen Collection subsection). Participants will also be encouraged to drink at least two glasses of water and consume a snack prior to each draw.

**Activity:** Participants will be asked to provide IIHI.
**Risk(s):** Breach of confidentiality
**Risk Minimization:** All IIHI and self-report data will be securely stored in REDCap. Only the PI and study coordinator will have/authorize access to IIHI and unique identifiers (*e.g.,* subject ID numbers) linking participants to de-identified data. Behavioral data, fMRI scans, and blood samples will be identified by subject ID numbers only and will stored separately from IIHI. Published data will in no way identify individual participants or disclose their identities.

**Activity:** Answering questions (via self-report) regarding personal history or current health status, especially with regard to psychobehavioral functioning.
**Risk(s):** Possible invasion of privacy or probing of information which might be considered sensitive
**Risk Minimization:** All members of the research team will be sensitive to the needs of participants by reminding them that they do not need to answer any questions that they would prefer not to answer, complete any tasks that they would prefer not to complete, or follow through with any procedure that they would rather decline. Study staff will use their clinical judgment to discontinue assessment if a participant appears upset.

Notably, suicidal ideation is probed in the BDI-II (item 9). Endorsement of any response other than a 0 (indicative of no suicidal ideation) will automatically prompt an email alert to the PI, the study coordinator, Edith Cloyd, JD, MSN, PMHNP-BC (psychiatric nurse practitioner who has 12+ years of experience diagnosing and treating people with a wide range of psychiatric disorders, including depression), and Landrew Sevel, Ph.D., clinical psychologist at the Osher Center. Follow-up to assess risk and clarify an action plan for protecting the participant will occur within 24 hours and is detailed in the attached suicide safety plan.

**Activity:** Completion of an eight-week psychobehavioral intervention.
**Risk(s):** Risks associated with psychotherapy are minimal. Participants may experience discomfort while talking about their symptoms, emotions, experiences, or daily routines. They may experience clinical worsening as they attempt to make any recommended behavioral changes.
**Risk Minimization:** Intervention facilitators will be sensitive to the needs of participants and available for support by phone on a daily basis, if needed. Weekly, the study medical monitor (Edith Cloyd, JD, MSN, PMHNP-BC) will review participants' medication status and depressive and/or anxious symptom scores and ensure referral to appropriate care for those who show evidence of substantial worsening.
**Activity:** Administration of visual or auditory stimuli related to cognitive/emotional functions, including the use of words with negative affective valence, which may be emotionally-charged in content and relate to themes that patients with affective disorders often express. Control words will be affectively neutral and matched for word length, number of syllables, etc. with emotionally-laden words.
**Risk(s):** Some stimuli may be perceived as distressing by a given participant due that participant's underlying perceptual or emotional impairment.
**Risk Minimization:** Stimuli will be thoroughly vetted by the research team. If the PI thinks that exposure to certain stimuli would be troubling or clinically inadvisable to a certain participant, s/he will not participate in this portion of the study. Those who partake in these tasks will always be monitored and the experimental session will be discontinued if a participant is noticeably uncomfortable or if s/he reports wishing to stop for any reason.

**Activity:** fMRI

**Risk(s)/Risk Minimization:**

(1) *Claustrophobia:* Despite efforts to ensure participants' comfort during scanning time (e.g., through staying in constant communication, minimizing the amount of time in the scanner, etc.), those who have claustrophobia may experience distress or perturbation of their psychiatric illness as a result of being confined and tasked to remain still in the scanner.
*Risk Minimization:* Prospective participants who disclose a history of claustrophobia will be excluded from the study.

(2) *Pregnancy:* There are no known risks of having MRI scans without contrast while pregnant; however, there may be risks that are unknown.
*Risk Minimization:* Prospective participants who are currently pregnant will be excluded from the study. Female participants of childbearing potential will take a urine test on the day of scans and be withdrawn from the study if pregnant.

(3) *Routine MRI Contraindications:* The magnetic field created by the scanner may interfere with the functioning of electromechanical devices (e.g., pacemakers) or cause temperature elevation in adjacent tissues in participants with implanted metal parts, including hip replacements, surgical clips, or metallic implants/fragments.
Risk Minimization: Participants will be carefully screened for all of the aforementioned, both at prescreen and on the day of scans, and excluded from the study.

(4) *Collision Hazard:* Because there is a strong magnetic field surrounding the scanner, there is potential for a metallic object to project toward the scanner and collide with a study participant. Such a collision could cause serious injury.
*Risk Minimization:* Participants and personnel will be carefully screened and instructed to remove all metal from their clothing/pockets and from their person before entering the scanning environment.

(5) *Noise:* The scanner produces tapping sounds during operation, which may reach very loud levels.
*Risk Minimization:* Participants will be provided with disposable earplugs that suppress external noise levels but do not eliminate voice communication with the scanner operator. In some cases, participants may use headphones instead, which will deliver other sounds and suppress scanner noise. If the participant finds the scanner noise objectionable, s/he can stop the study at any time.

(6) *Neurostimulation:* Due to the rapid switching of magnetic field gradients used in scanning, it is possible for participants to experience neurostimulation effects, such as muscle twitches and tingling sensations. Stimulation of the muscles of the heart, causing an abnormal heart rhythm, is much less likely to occur.
*Risk Minimization:* There are no known risks associated with these effects. The machines used in this research create magnetic field gradients within acceptable limits specified by the FDA.

(7) *Change in Body Temperature:* A slight, but not serious, increase in body temperature may occur in the presence of radiofrequency waves.
*Risk Minimization:* A significant, deleterious increase in temperature is extremely unlikely at the

settings employed in this study, which are within FDA guidelines.

(8) *RF Antenna Effects:* If metal wires or electrodes are attached to a participant's skin, radiofrequency signals from the scanner could induce sufficient electrical currents in the wires to cause burns.
*Risk Minimization:* If metal wires or electrodes are present, the scanner operator will inspect and arrange them to reduce potential for induced currents.

(9) *Quench Hazard:* The scanner uses liquid nitrogen and/or liquid helium to maintain the magnet's superconductivity. In the very remote event that the magnet quenches (loses its superconductivity), the liquid nitrogen and helium will boil off rapidly. Gaseous nitrogen and helium can be dangerous if breathed for more than a few moments.
*Risk Minimization:* Noxious gases would be vented to the outside of the imaging facility, per the design of the scanner. Oxygen monitors are present as an additional precaution. If necessary, the scanner operator will be present to provide immediate assistance to anyone inside/evacuate the scanning room.

(10) *Incidental Findings:* Although the pulse sequences used in this study are not those used for clinical diagnostic purposes, there is slight potential for incidentally uncovering structural brain pathology.
*Risk Minimization:* In the event an abnormality is detected by researchers or the scanning operator, the scans will be further examined by a radiologist and the PI may encourage the participant to consult his/her physician.

## 7.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Participants could react adversely during the assessment and/or intervention procedures or symptoms could worsen during the course of the study (although this worsening may or may not be related to the treatment). Once weekly during the eight-week MBCT or MBSR intervention, participants will complete a brief medication questionnaire, the Beck Depression Inventory-II, and the Spielberger State-Trait Anxiety Inventory. The PI and study coordinator will examine weekly medication status and symptom scores with the appointed study medical monitor (Edith Cloyd, JD, MSN, PMHNP-BC) and note changes. If we see evidence of substantial worsening, at-risk participants will be removed from the study and appropriate safety measures will be taken. Dropout rates will be examined at least quarterly, depending on enrollment. If there are concerns about attrition, the research team will review information regarding each participant who withdrew and study procedures, and ensure adequate subject protection and data integrity.

Reporting of adverse events will occur as follows:

During the study, if patients become unstable, Eydie Cloyd, the Psychiatric mental health nurse practitioner, will be monitoring clinical change and risk of suicidality.

Any serious adverse event (e.g., death, suicide attempt, hospitalization) will be reported by telephone within 24 hours to the IRB and the DSMB. A full written report of the event will be sent to these entities within 24 hours of the event's occurrence.

Any moderate adverse event (e.g., causing interference with usual activities or requiring treatment) and which appears definitely, probably, or possibly related to study participation will be reported to the IRB and DSMB in writing within seven working days. Any mild adverse event will be summarized in the IRB annual progress reports.

## 8.0 Study Withdrawal/Discontinuation

**Criteria for study termination**

Patients will be terminated from the study if they meet the following criteria:

1) Patient exhibits psychopathology requiring changes in medication dosage or type
2) Patient requires inpatient hospitalization or medication
3) Patient becomes medically unstable and necessitates intensive medical intervention as determined by the patient's physician
4) Patient becomes suicidal as determined by MBI instructors and requires inpatient hospitalization or more intensive treatment
5) Patient misses more than 50% of MBI sessions (determined to be an adequate dose)(Crane and Williams 2010).

Patients terminated because of exacerbation of symptoms will be considered treatment non-responders, whereas patients terminated due to medical problems or suicidality may participate again once they are medically and psychologically stable. They will be enrolled in a subsequent group at a later time.

## 9.0 Statistical Considerations

**Power analysis.** Presently, no studies have explored P1 ERP activity in anxious populations before and after an MBCT intervention, so no direct estimation of effect size is available. However, Schoenberg et al.[54] conducted a study in which ADHD-related ERP markers were monitored before and after an MBCT intervention. Therefore, mean amplitude differences and standard deviations from the study were used to determine the sample size for the proposed research. An a priori power analysis conducted using PASS version 11 software indicated that a minimum of 34 patients are needed to reject the null hypothesis with 80% power at a type I error rate of 0.05. Accounting for 18% attrition, 42 patients will be recruited in total for the Anxiety Arm.

A repeated-measure ANCOVA of pre- and post-treatment fMRI data will be performed to quantify the MBCT group and test Hypothesis 1(a) [*Target engagement will be identified through a significant interaction (post vs. pre-intervention; negative vs. neutral words; NoGo vs. Go) involving critical nodes of the fronto-parietal control network (dACC, FPC, AI) and decreased activation in limbic regions (hippocampus, amygdala)*]. A classical fixed sample trial design was conducted to determine a sample size that provides a Type I error of no more than 5% and a statistical power of no less than 80%. Based on the pre- and post-treatment fMRI brain imaging data of 10 borderline personality disorder patients for a design of 2 time points and 1 key condition contrast ([(Negative vs Neutral) x (No-Go vs Go)] undergoing the same Go-NoGo Emotional Word paradigm we are using in this study) with the differential BOLD response ***effect size at 1.963, and 0.274 for the 2 time points*** observed in the right amygdala region (ROI with relatively small effect size), **a sample size of no less than 25 (21 for a statistical power of no less**

**than 80%)** is needed for each group if the BOLD response reduction in PE group is no more than 40%. The above analysis was performed using the PASS version 11 (NCSS Statistical Software, Kaysville, UT). Random effects models employed in the proposed fMRI study have demonstrated to require a sample of 15 – 20 subjects per group to attain sufficient statistical power to detect a relatively small effect size.(Lazar 2008) We have repeatedly demonstrated employing longitudinal-based within(Butler, Pan et al. 2007) and between(Perez, Pan et al. 2015) groups designs that sample sizes ≥ 15 (per group) can identify the neural mechanisms supporting treatment-related outcomes. The proposed sample size (n=26) will be recruited for the Depression Arm.

Power analyses for behavioral testing only were estimated using G*Power software.(Faul, Erdfelder et al. 2009) Effect estimate (0.62) was based on previous use of the go/no-go testing pre/post-mindfulness training.(Loucks 2017) We performed the power calculation with 4 assessment points, and alpha=0.05. The proposed sample size (n=30) for the high stress/chronic pain Arm is sufficient to result in power of 0.80 with an effect size of 0.62.

## 10.0 Privacy/Confidentiality Issues

We will make every reasonable effort to protect the privacy and confidentiality interests of research participants

**Follow-up and Record Retention**

Based on our current and projected internal resources, we anticipate needing three years, total, to conduct this pilot study from enrollment through future grant preparation and potential dissemination of pilot data.

PHI will no longer be accessed upon closure of the study. Within 5 years of closure of the study, database will be destroyed through permanent erasure.

**13. REFERENCES.**

Butler, T., H. Pan, O. Tuescher, A. Engelien, M. Goldstein, J. Epstein, D. Weisholtz, J. C. Root, X. Protopopescu, A. C. Cunningham-Bussel, L. Chang, X. H. Xie, Q. Chen, E. A. Phelps, J. E. Ledoux, E. Stern and D. A. Silbersweig (2007). "Human fear-related motor neurocircuitry." Neuroscience **150**(1): 1-7.
Carver, C. S. and T. L. White (1994). "Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales." Journal of Personality and Social Psychology **67**(2): 319-333.
Crane, C. and J. M. G. Williams (2010). "Factors Associated with Attrition from Mindfulness-Based Cognitive Therapy in Patients with a History of Suicidal Depression." Mindfulness **1**(1): 10-20.
Faul, F., E. Erdfelder, A. Buchner and A.-G. Lang (2009). "Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses." Behavior Research Methods **41**(4): 1149-1160.
Kabat-Zinn, J. (1982). "An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results." Gen Hosp Psychiatry **4**(1): 33-47.
Lazar, N. (2008). The Statistical Analysis of Functional MRI Data. New York, New York, Springer.
Loucks, E. P. (2017). Mindfulness Influences on Self-Regulation: Mental and Physical Health Implications.
Perez, D. L., H. Pan, D. S. Weisholtz, J. C. Root, O. Tuescher, D. B. Fischer, T. Butler, D. R. Vago, N. Isenberg, J. Epstein, Y. Landa, T. E. Smith, A. J. Savitz, D. A. Silbersweig and E. Stern (2015). "Altered threat and safety neural processing linked to persecutory delusions in schizophrenia: a two-task fMRI study." Psychiatry Res.
Segal, Z. V., J. M. Williams and J. D. Teasdale (2013). Mindfulness-Based Cognitive Therapy. New York, NY, The Guilford Press.
Vago, D. R. and D. A. Silbersweig (2012). "Self-Awareness, Self-Regulation, and Self-Transcendence (S-ART): A Framework for Understanding the Neurobiological Mechanisms of Mindfulness." Frontiers in Human Neuroscience **6**: 1-30.