Neural Mechanisms of Mindfulness-based Cognitive Therapy (MBCT) for Posttraumatic Stress Disorder (PTSD)

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Amendments

Date	Version	Section(s)	Changes
1/24/2020	1.3	5.4, 5.6	A change made to improve feasibility and increase accrual and decrease unacceptable wait times for patients enrolled in the study. We have changed recruitment to allow participants who consent but are later found to be unable to do fMRI or are missing 1 PTSD symptom to be allowed to do just the psychotherapy group and follow-up assessment.

ABBREVIATIONS

AAQ – Acceptance and Action Questionnaire

BOLD – blood oxygen level dependent

BPI – Brief Pain Inventory

CAPS-5 – Clinician-administered PTSD Scale

CEN – Central Executive Network

CEN – central executive network

CGI – Clinical Global Impressions Scale

Cx - criteria

CTQ – Childhood Trauma Questionnaire

dACC – dorsal anterior cingulate cortex

DAN – dorsal attention network

DMN – default mode network

EQ – Experiences Questionnaire-Decentering Factor

ERQ – Emotional Regulation Questionnaire

FEF – frontal eye field

fMRI – functional magnetic resonance imaging

GAD – generalized anxiety disorder

HAM-D – Hamilton Depression Rating Scale

HIPAA – Health Information Portability and Accountability Act

ICN – intrinsic connectivity network

IFG – inferior frontal gyrus

IRBMED – Institutional Review Board for Michigan Medicine

LEC – Lifetime Events Checklist

MBCT – Mindfulness-based Cognitive Treatment

MBI – Mindfulness-based intervention

MBSR – Mindfulness-based Stress Reduction

MDD – Major Depressive Disorder

MFG – middle frontal gyrus

MINI – Mini-International Neuropsychiatric Interview

MMQ-15 – Multifacet Mindfulness Questionnaire

MRG – Muscle Relaxation Group

MTG – middle temporal gyrus

n/a – not applicable

PCC – posterior cingulate cortex

PCC-dlPFC – posterior cingulate cortex -corsolateral prefrontal cortex

PCL-5 – PTSD Checklist

PHQ-9 – Patient History Questionnaire

PPC – posterior parietal cortex

PTSD – Posttraumatic Stress Disorder

RCT – randomized controlled trial

rsFC – resting state functional connectivity

RSQ-RRS – Response Styles Questionnaire, Ruminative Response Subscale

S – study-paid activity with efforted staff

sgACC – subgenual anterior cingulate cortex

sgPFS – subgenual prefontal cortex

SN – salience network

SPL – superior parietal lobule

Sx – symptoms

VA – Veteran's Affairs (Ann Arbor Medical Center)

VAN – ventral attention network

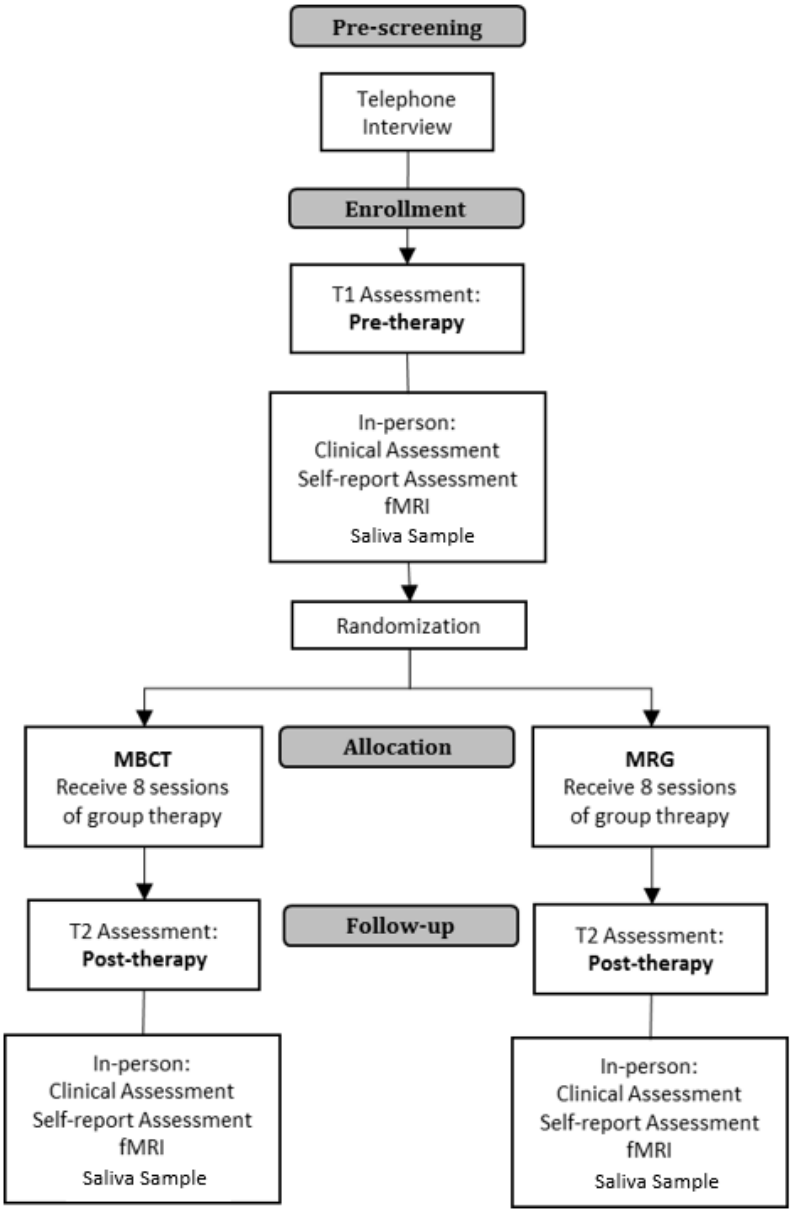
vmPFC – ventromedial prefrontal cortex

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Neural Mechanisms of Mindfulness-based Cognitive Therapy (MBCT) for Posttraumatic Stress Disorder (PTSD)
Study Description:	A parallel group randomized controlled trial examining the mechanisms underlying mindfulness-based cognitive training (MBCT) for posttraumatic stress disorder (PTSD)
Primary Objective	To show an increase in the resting state functional connectivity between the posterior cingulate cortex (PCC) and the dorsolateral prefrontal cortex
Secondary Objectives	To show a decrease in the resting state functional connectivity between the Insula and the posterior cingulate cortex (PCC)
Study Population:	Adult patients with PTSD able to attend therapy sessions in SE Michigan
Phase:	n/a
Description of Sites/Facilities Enrolling Participants:	Participants will be enrolled by the University of Michigan; study interventions will take place at various locations around campus and the greater Ann Arbor and Southeastern Michigan area; fMRI scans will take place at Functional MRI Laboratory on North Campus
Description of Study Intervention:	Both study interventions (mindfulness-based cognitive training and muscle relaxation therapy) involve 8 weeks of group therapy, and include in-session exercises and daily at-home practice.
Study Duration:	20 months
Participant Duration:	8 weeks of intervention plus 4 days of assessments; total time enrolled in study will depend on accrual and randomization rates

1.2 CONSORT SCHEMA



1.3 SCHEDULE OF ACTIVITIES

	OnCore Segment		Consented/On Study			On Arm/On Treatment								Off Study	
	Study Timeline	Pre-study	Pre-therapy[1] [T1]			8 sessions of group therapy[2]								Post-therapy[3] [T2 and T3]	
	Notes		Occurs on 2 different days			Scheduled for consecutive weeks; start date depends on enrollment numbers because study is randomizing in groups								T2 w/MRI scan T3 no MRI scan	
Initial Interview	Pre-screening (for PTSD)	S													
Consent –	Consent		S												
	Eligibility Criteria Review		S												
Clinical Assessments –	MINI		S											S	
	LEC		S											S	
	CAPS-5		S											S	
	HAM-D		S											S	
Intervention[4]	MBCT or MRG				S	S	S	S	S	S	S	S			
	PHQ (and CSSRS as needed)				S	S	S	S	S	S	S	S			
	PCL-5				S	S	S	S	S	S	S	S			
	PTCI-9				S	S	S	S	S	S	S	S			
	SCS				S	S	S	S	S	S	S	S			
	CGI				S	S	S	S	S	S	S	S			
fMRI[5] -	fMRI screening			S											S
	Pregnancy test (dipstick)			S											S
	Resting connectivity			S											S
	Self-related processing task			S											S
Biomarkers[6]	Saliva for adrenergic & inflammatory function & DNA (optional)		S											S	
Psychological & QOL Self-Report Assessments at University of Michigan	EQ		S											S	
	AAQ		S											S	
	MMQ-15		S											S	
	ERQ		S											S	
	SCS		S											S	
	RSQ-RRS		S											S	
	BPI		S											S	
	PCL-5		S											S	
	BDI-II		S											S	
	PTCI-9		S											S	
	CTQ		S												

[1] Baseline testing occurs pre-therapy and will take place over 2 (not necessarily consecutive) days; it is designated as T1
[2] Participants are randomized after completion of all pre-therapy assessments; therapy will not begin until sufficient number of participants are available to randomize as a group.
[3] Post-testing occurs upon completion of therapy sessions and will also take place over 2 (not necessarily) consecutive days; it is designated as T2
[4] The PHQ and CGI will be administered during each therapy session as safety assessments; the CSSRS will only be administered if warranted based on PHQ responses
[5]Participants will be scheduled for the fMRI at the North Campus Functional Imaging Laboratory.
[6] Saliva samples will be obtained at the UM fMRI facility and stored for batch analysis.
[7] The timing of randomization relative to T1 assessments will depend on enrollment; participants will be block randomized to one group therapy or another; it's important to maintain some participant homogeneity within the each 8-week therapy group (i.e. combat trauma vs. interpersonal trauma, etc.).

2 INTRODUCTION

2.1 STUDY RATIONALE

Posttraumatic stress disorder (PTSD) is common, can be chronic and debilitating, and is associated with high costs to individuals and society. Existing trauma exposure-based psychotherapies show high efficacy, but a recent meta-analysis reported the surprising finding that 30-50% of PTSD patients treated do not show clinically meaningful improvement$_1$, suggesting "one size may not fit all" and that additional approaches are needed. In recent years, mindfulness-based approaches like Mindfulness-based Cognitive Therapy (MBCT) have emerged as cost-effective, accessible and effective interventions for PTSD[2], with recently increasing utilization as population-based interventions for PTSD, warranting more research on mechanisms. Accumulating evidence suggests the construct of decentering as a primary psychological process involved with MBCT. Decentering, defined as the metacognitive capacity to observe thoughts, feelings, memories, and bodily sensations with healthy psychological distance and decreased reactivity, is thought to help resolve the automatic negative cognitive-affective responses that typify symptoms in depression and PTSD. There is increasing interest to understand neural targets and mechanisms underlying MBCT and decentering, and whether these are shared with or distinct from targets of other psychotherapy components (and thus potentially complementary). This knowledge will allow optimization of effective therapy components.

There is mounting evidence that dysfunction in large-scale distributed neural connectivity networks may underlie psychopathology like PTSD and MDD, and that treatments, including MBCT, target strengthening compensatory mechanisms that normalize function of core aberrations within and between these networks. Changes in the Default Mode Network (DMN, e.g. ventromedial prefrontal cortex [vmPFC], subgenual ACC), the Central Executive Network (CEN, dlPFC, parietal cortex), and the Salience Network (SN, e.g. insula, amygdala) may underlie decentering and effects of MBCT. We and others report mindfulness-linked increased functional DMN-CEN connectivity[2,3,4] (e.g., posterior cingulate cortex [PCC] with bilateral dlPFC) that was associated with decreased PTSD symptoms$_2$ and decreased plasma inflammatory markers (IL-6)[3]. Mindfulness may also decrease connectivity between SN and DMN (insula-vmPFC), and increase SN-CEN connectivity (insula-dlPFC)[5]. We need to determine whether these effects on DMN, CEN, and SN networks are in fact primary targets of MBCT that can mediate mental and physical health-related outcomes.

2.2 BACKGROUND

2.2.1 Clinical Significance

A considerable proportion of trauma exposed individuals go on to suffer from posttraumatic stress disorder (PTSD) or major depression (MDD). These conditions also show high levels of co-morbidity with one another. Trauma-related psychiatric disorders are common and highly debilitating disorders associated with immense levels of human suffering and socioeconomic costs[7,8]. For instance, PTSD has lifetime prevalence of ~10% in the general population and higher in subpopulations (e.g. up to 20% in combat veterans[9-11] and up to 45% in low SES people living in urban areas[12]. PTSD has high levels of disability and family disruption that can last for decades[10,11,13-15]. Similarly, MDD is very common with a lifetime prevalence of ~16%[8]. Chronic depression is a leading cause of disability, associated with

notoriously high levels of relapse[16]; and is often associated with trauma; the combination of chronic PTSD and chronic depression can be particularly difficult to treat. Although existing trauma-focused exposure therapies such as Prolonged Exposure (PE) show high levels of efficacy in randomized controlled trials (RCTs)[1,17-20], recent meta-analyses[1] report 30-50% of patients treated do not show clinically meaningful improvement and 62-70% of patients retain their PTSD diagnosis. Additional treatment modalities are needed for both PTSD and MDD, and there is particular interest in interventions that may provide orthogonal or complementary effects with existing treatment approaches to maximize optimal outcomes. Recently, mindfulness based cognitive therapy (MBCT), an intervention originally designed and evaluated for the prevention of MDD relapse, has emerged as a treatment modality with high levels of acceptability in PTSD[21-25] that may be useful as an adjunctive treatment or alternative for patients who decline first-line treatments.

2.2.2 Mindfulness-based Cognitive Therapy (MBCT)

MBCT is an 8-week group "Mindfulness-based intervention" (MBI) group psychotherapy based on Mindfulness-based Stress Reduction (MBSR). MBCT was initially developed for preventing relapse in remitted patients with MDD, and a number RCTs and recent meta-analysis suggest high level of efficacy for preventing depression relapse[16,26,27]. MBCT incorporates many elements of MBSR, the prototypic "MBI", including exercises for enhancing sensory, interoceptive, and proprioceptive attention (e.g. raisin exercise, bodyscan, and mindful movement), and meta-cognitive awareness / mindfulness of breath and experiential engagement and acceptance of sensations, emotional states, and thoughts. MBCT combines these with cognitive therapy exercises, including psychoeducation and emotional recognition exercises (e.g., pleasant and unpleasant events calendars). It includes both in-session and daily at home practice, as well as "mindful inquiry" in each session, inviting patients to discuss their experiences with mindfulness exercises and how they find these relevant to mental health and depression, and helping to recognize and not get "stuck" in automatic, depressogenic patterns of thought and rumination.

Findings consistently indicate that MBCT and MBSR are well tolerated and demonstrate efficacy for PTSD in studies of both primarily males with combat trauma[2,24,25,28-32], and primarily females with adult[22] and childhood[23,33] interpersonal violence and sexual abuse. MBCT / MBSR also shows efficacy for other acute psychiatric disorders, as an adjunctive treatment for treatment refractory major depression[34-36] and for generalized anxiety disorder[37-39].

2.2.3 Role of Alterations in Large-Scale Neural Networks in Trauma-related Psychopathology

Mounting evidence from basic, translational, and treatment research converges on the view that neural underpinnings of psychiatric disorders like PTSD and MDD may be better understood by dysfunctions in relationships between large-scale neural networks[40-43] rather than micro-circuit "locationist" approaches. Resting state functional connectivity (rsFC) analyses find multiple large-scale intrinsic connectivity networks (ICNs), distributed brain networks at rest that correspond to task-related connectivity patterns[44,45]. A comprehensive description is not possible here, but the ICNs relevant to the nature and treatment of PTSD include the "task-negative" Default Mode Network (DMN), with nodes in the posterior cingulate cortex (PCC), ventral medial PFC (vmPFC), and subgenual PFC (sgPFC) associated with social cognition, self-referential processing, autobiographical memory, and "mind wandering", the Salience Network (SN), with nodes in insula, dorsal anterior cingulate (dACC) and amygdala, associated with detection of salience and threat and integration of interoceptive, autonomic, and emotional information. Several conectivity networks have been proposed underlying attention and executive /

cognitive control. The Dorsal Attention Network (DAN), frontal eye field (FEF), superior parietal lobule (SPL), is involved in with voluntary deployment of attention and externally-directed cognitions, and the Ventral Attention Network (VAN), right inferior frontal gyrus (IFG), middle temporal gyrus (MTG) involved reorientation to unexpected events. The Central Executive Network (CEN) or Fronto-Parietal Control Network (FPCN), bilateral dlPFC and posterior parietal cortex (PPC), is involved in executive functions and "top-down control". The CEN appears to play a central role in regulating and directing distributed systems according to current task goals[42], for example, CEN regulates normally anti-correlated activity in DMN and DAN[46], and coordinates with DAN in maintaining voluntary internal trains of thought[47]. The dACC also plays important roles in cognitive conflict and error detection and some reports find dACC within cognitive control networks[48,49] as well as SN.

Several research groups, including our own lab, report that individuals with PTSD evidence hyper-connectivity within SN (e.g. amygdala-insula)[50-53], and aberrantly increased DMN-SN (e.g. DMN-amygdala and insula) cross-network connectivity / desegregation[52,54,55]. By contrast, individuals with PTSD evidence decreased within-network DMN connectivity (PCC-vmPFC and PCC-hippocampus)[52,55,56], and decreased vmPFC-hippocampus connectivity[52,53,57]. We hypothesized increased DMN-SN connectivity at rest as potentially underlying PTSD hyperarousal symptoms, associated with intrusive, automatic distress reactions to both external cues and internal physiological states. Intriguingly, we have also found self-reported rumination correlates with PCC-insula connectivity, and PTSD avoidance symptoms negatively correlate with the strength of PCC-dlPFC connectivity. Similar dysfunctional vmPFC-insula hyperconnectivity has also been implicated in depression and anxiety[58], which is proposed to lead to negativity bias and self-referential misinterpretation and amplification of interoceptive signals. Abnormalities in ICNs are also seen in MDD. In contrast to PTSD, hyperactivity in DMN has been reported in MDD, and in particular increased connectivity between PCC and subgenual ACC (sgACC)[43,59] which has been though to reflect depressive rumination in the scanner[43,59,60]. Recent whole-brain connectomic studies in rumination induction also find exaggerated DMN sgACC[61]. MDD is reported to show decreased DMN connectivity with dorsal attention network (DAN)[62], and decreased connectivity between posterior DMN and dorsal CEN, including dlPFC[63,64] consistent with the notion of difficulty in switching from internalized, self-referential states in which the DMN is dominant, to an "executive state" in which the CEN is dominant and attention is directed toward external stimuli[43].

2.2.4 Changes in Functional Connectivity Networks in Mindfulness Training

Emerging evidence indicates that psychotherapies such as MBCT and mindfulness practice may exert their salutary effects by directly restoring dysfunctional networks, and by engaging compensatory effects on networks that modulate the dysfunctional relationships. A handful of studies have examined the acute and enduring effects (equivalent to the intensity and duration in MBCT) of mindfulness practice (assessed via fMRI) on functional connectivity in a priori nodes within networks. For example, Hasenkamp et al. reported four mental states in mindfulness experts during in-scanner mindfulness practice associated with differential activations,[65] and also with different neural connectivity networks at rest[66]: mind wandering with DMN, awareness of mind wandering with SN, focus on the present experience with dlPFC (CEN), and shift of attention back to focus on present experience with dlPFC and PPC, suggesting the involvement of executive / control networks in mindfulness practice. Using a whole-brain connectomic approach, we also find increased connectivity in DMN-DAN connectivity when people with no mindfulness training perform a mindfulness task in the scanner. Several studies of effects of longer-term mindfulness practice, including mindfulness intervention like MBCT, implicate enduring

changes in increased connectivity between DMN and CEN (dlPFC). The PI, King, et al., recently reported that a 16-week group intervention with mindfulness training (based on MBCT) in PTSD patients led to increased DMN-CEN connectivity (i.e. PCC seed connectivity with bilateral dlPFC)[2]. Furthermore, the PCC-dlPFC connectivity was associated with decreases in PTSD avoidance and hyperarousal symptoms. Consistent with our findings, Brewer et al. found highly similar PCC-DLPFC and PCC-dACC connectivity increases in long-term meditators[4], and Creswell et al. found highly similar PCC-dlPFC increases following a 3-day intensive mindfulness training[3] that correlated with decreased plasma IL-6 3 months later. They also found increased resting connectivity between the dlPFC seed (CEN) and both DAN (superior parietal lobule, supplementary eye field, MFG) and VAN (right IFG, MTG) regions, suggesting mindfulness training leads to greater coordination / integration between CEN, DAN, and VAN, and that increased executive / attentional capacity may lead to greater capacity for salutary emotional regulation. Accumulating evidence indicates that MBCT / mindfulness training may decrease connectivity between DMN and SN. While interoception and both acute mindfulness[65] and MBSR[5] all lead to increased activity in insula (SN), Farb et al. report MBSR and mindfulness training also lead to decreased coupling between DMN and SN (i.e. vmPFC-insula)[5], and suggested this "uncoupling" of vmPFC and insula leads to less automatic negative appraisals and cognitions. Further consistent with this, Creswell et al. report that a brief intensive mindfulness training led to decreased amygdala-sgACC connectivity[67], providing further evidence that MBCT might decrease SN-DMN connectivity as well as increase DMN-CEN connectivity.

2.2.5 Mindfulness, Decentering, Metacognitive Awareness, and Related Psychological Processes Potentially Mediating Effects of MBCT

Beyond the considerable clinical efficacy indicating that MBCT reduces depression symptoms, mindfulness interventions also appear to act upon theoretically predicted psychological processes, including decreased rumination, worry, and emotional reactivity, and increases in various self-report measures mindfulness, meta-awareness and decentering, and self-compassion (for meta-analyses/reviews[16,68-70] that may mediate the therapeutic effects of MBCT. Low levels of decentering are associated with anxiety and depression symptoms and psychosocial disability[71,72]. There is accumulating evidence that changes in these psychological processes (e.g., mindfulness, decentering / meta-awareness, negative reactivity, and rumination and worry (reviewed[70,73]) statistically mediate the clinical efficacy of MBCT / MBSR. Two recent studies report decentering statistically mediates therapeutic effects of MBSR on anxiety[74] and mediates effects of mindfulness on depression by complementary mediation and indirect-only mediation[75]; thus suggesting decentering as a psychological process mediating therapeutic effects of MBCT. Decentering can be defined as a metacognitive capacity of individuals to observe mental phenomena as they arise in the mind (e.g., thoughts, feelings, memories, etc.) as transient psychological events rather than necessarily as "facts" i.e. inherent aspects of the self or accurate representations of reality[72,76,77]. Thus decentering allows for appropriate psychological distancing and disengagement from, and decreased "over-personalization" of negative internal experiences, and thus is expected to result in decreased negative reactivity to thoughts[76].

2.3 Specific Aims

We will use 3T fMRI paradigms: resting state functional connectivity (rsFC), psycho-physiological interaction (PPI), and powerful whole-brain connectomics methods (e.g. joint independent components

analysis, ICA) to identify effects of MBCT on connectivity during rest and self-related tasks compared to MRG:

- To evaluate rsFC using seed-based (PCC, vmPFC, insula, dlPFC) and whole-brain connectomics analyses in MBCT vs. MRG. We hypothesize that MBCT will increase DMN-CEN (PCC-dlPFC) connectivity.
- To evaluate self-related processing using self-relatedness vs. momentary experience task[5], using PPI and whole brain connectomics. We hypothesize that MBCT will decrease DMN-SN (vmPFC-insula) connectivity.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

Psychotherapy groups and Psychological assessment. It is possible that any psychotherapy or psychological assessment may increase distressing thoughts and nightmares about an individual's past trauma. Likewise, participants might feel uncomfortable disclosing distressing thoughts in front of others during therapy. Safeguards are in place to protect against this risk – participants will have weekly contact with therapists, and will also complete brief symptom self-report measures as part of each session. The therapist will review these forms each session for risk factors and clinical worsening. If deemed at acute risk the therapist will schedule an individual meeting for further assessment. All assessments and therapy sessions are conducted in private rooms (i.e. with a door that closes, used by one person or group at a time).

Magnetic Resonance Imaging. Risks from the functional MRI scanner include minor risk of discomfort because of the prolonged supine position; and some individuals might feel anxious from being confined in the scanner. Other possible but extremely unlikely adverse effects include:

- Injury due to the main magnetic field attracting ferromagnetic/metallic objects whether inside the body or external to the scanner
- Temporary hearing loss due to loud noises associated with fMRI scanning
- Potential of exacerbated symptoms of PTSD when going into the fMRI
- Peripheral nerve stimulation (PNS) from the fast imaging sequences used in this study; this is described as light touching sensation on the skin surface and may cause mild discomfort, but is not harmful to the participant. The scanner is operated within FDA guidelines so the potential for inducing PNS is very low.
- Burns caused by wearing transdermal medication patches (because of the aluminized backing) during an MRI scan
- Incidental clinical findings of brain abnormalities (e.g. tumor) previously unknown to the participant

To reduce any potential risks, we will:

- Screen anyone allowed in the room for metallic objects prior to entering the scan room to minimize the risk of the main magnetic field attracting ferromagnetic/metallic objects towards the magnet.
- Screen for transdermal medication patches.

- Require participants to wear foam earplugs or other hearing protection, as is routine for clinical patients, to prevent risk of hearing damage due to the inherently loud noise of MR scanning.
- Use custom pads and pillows to make participants as comfortable as possible.
- Tell participants that they can talk with the operator or researcher through an intercom at all times, and that they can able to trigger an audible alarm for immediate attention or to get out of the MRI machine.
- Notify the participant if an abnormality is detected on an MRI image. While the research team is not formally trained to diagnose brain abnormalities from MRI images, they can help advise participants on appropriate follow-up actions.

Video & Audio recording. All therapy sessions will be recorded. While the recording equipment will be trained on the therapist, it is likely that participants' voices will be audible. This means there is a chance that someone could be identified by their voice alone. Recordings are considered part of the research record and will be afforded the same level confidentiality. The recordings are not transcribed, but rather reviewed for therapist compliance with the intervention. The video files will be stored on Michigan Medicine servers and will be available only to authorized study staff (via access restrictions and password protections).

Genomic analysis. There are no physical risks associated with the collection of saliva for the genomic analysis portion of the study. . There is a risk are associated with a potential confidentiality breach (very rare) whether by accident or because the researchers publish information about the groups to which a particular subject might belong (e.g. sex and gender, age, racial and ethnic groups). Preserving data integrity and the separation of identifying factors from genetic data will be accomplished by:

- Labeling each sample with a unique code rather than personal information
- Use password protections and access restrictions to authorized users only
- Only share information with authorized users for approved purposes

Additionally, the participant and their data are protected by the Federal genetic non-discrimination law (GINA) and an NIH-issued Certificate of Confidentiality.

Privacy and Confidentiality. There is a risks to a participant's privacy associated with any research study or clinical interaction with the health system. The nature of group therapy involves sharing personal thoughts in the presence of others. The treating therapists will instruct group members to respect the privacy of their fellow participants. All participant interactions with the study team member (e.g. phone screenings, study visits, therapy sessions) will be conducted in private space. The information collected for this study will stored in a HIPAA-compliant database housed on Michigan Medicine servers; access will be restricted based on study role and job responsibilities. Hard copies of case report forms, informed consent documents, etc. will be stored in a double locked environment.

2.4.2 Known Potential Benefits

Participants will be informed that while it is possible that some participants may derive benefit from the study interventions ("mindfulness training" or muscle relaxation) or participation in the study alone, the primary purpose of the study is to improve our scientific understanding of mindfulness training and PTSD which could benefit others with PTSD. Participants may experience satisfaction of knowing that they have contributed to science.

2.4.3 Assessment of Potential Risk & Benefits

This research will generate new knowledge about brain activity associated with effective treatments for PTSD. The improved understanding of such neural mechanisms is expected to direct development of targeted PTSD treatments, ultimately improving social functioning and quality of life of people with PTSD. The risks are comparable to those ordinarily encountered during routine mental health and medical examination, and the knowledge to be gained weighs favorably against these risks.

3 OBJECTIVES AND ENDPOINTS (GO/NO-GO CRITERIA)

Primary Objective	Endpoint/Outcome	Timeframe
Change in resting state functional connectivity between the PCC and dlPFC by the MBCT group compared to the MRG	Statistically significant increase in PCC-dlPFC functional connectivity (effect size d>0.60)	Post-treatment (after 8-weeks of therapy)
Secondary Objective	**Endpoint/Outcome**	**Timeframe**
Change in resting state functional connectivity between Insula and PCC by the MBCT group compared to the MRG	Statistically significant decrease in Insula-PCC functional connectivity	Post-treatment (after 8-weeks of therapy)

4 STUDY DESIGN

4.1 OVERALL DESIGN

Study Design

- Mechanistic study
- Parallel groups randomized controlled trial

Study Arms

- Experimental Group: Mindfulness-based Cognitive Therapy
- Control Group: Muscle Relaxation

4.2 STUDY DESCRIPTION

This study is a randomized controlled trial evaluating underlying mechanisms of two different non-pharmacological therapies for PTSD. Our hypothesis, based upon our work[2] and that of others[3-6] is that alterations in default mode network (DMN), salience network (SN), and the central executive network (CEN) are central mechanisms underlying therapeutic effects of MBCT. We propose that MBCT leads to (i) increased DMN-CEN connectivity and (ii) decreased DMN-SN connectivity related to decentering and metacognitive emotional regulation. Our rationale is (i) increased DMN-CEN connectivity is linked to increased meta-cognitive attentional capacity, (ii) decreased DMN-SN connectivity is related to

increased ability to dispersonalize aversive cues and interoceptive signals and decreased negative reactivity to these signals.

Potential participants will complete a pre-screening interview with a research assistant for signs and symptoms of PTSD prior to enrollment in the study. Individuals passing this eligibility review will be scheduled for an in-person baseline evaluation (T1, pre-therapy) at our research lab. At this evaluation, individuals will complete the informed consent process and undergo a clinical intake assessment for PTSD and other eligibility criteria. If eligible and consented, participants will complete the remaining self-reported psychological and QOL assessments, undergo saliva collection for biomarkers and/or DNA, and an fMRI. The fMRI is typically scheduled for a subsequent day at the North Campus Functional MRI Laboratory (http://fmri.research.umich.edu/).

Participants will be randomized to a study arm with the goal running 8-12 treatment groups (MBCT or MRG) over the study period. Treatment groups will consist of a minimum of 4 people, preferably comprised of 5-8 individuals. After 8 consecutive weeks of treatment (at T2, post-therapy), participants will repeat the clinical and outcome assessments, including the fMRI.

Post-therapy assessments will mirror the pre-therapy assessments. Like at baseline, participants will complete the clinical and self-reported assessments on one day and the fMRI on a subsequent day.

4.3 Randomization

This study will use block randomization to assign people to a study arm. The study statistician is responsible for performing the randomization procedure and will be the sole holder of the key until the blind is broken. Randomization will occur once a sufficient number of participants have enrolled to ensure desired group size including withdrawals.

5 Study Population

The population under study includes male and female adults (aged 18-72 years) with PTSD who are willing to travel to study locations (e.g. Rachel Upjohn Building, North Campus fMRI lab, etc.) for multiple outcome assessments and treatment sessions. At the request of the sponsor we are excluding certain sub-types of PTSD based on the potential for different underlying neural mechanisms. Other than that, the eligibility criteria were minimalized to enhance generalizability.

The study sample will represent persons with PTSD living in the Ann Arbor/South East Michigan area. The incidence of PTSD is approximately twice as high in women as in men, and thus we do not anticipate difficulty in recruiting sufficient numbers of women. Based upon demographics of our geographic region, we expect our sample will be approximately 11% African America, 8% Asian American, 1% Native American, and 80% European American, and approximately 8% Hispanic ethnicity. An upper age limit will be set at age 60 because there is evidence that neurocircuitry of a range of cognitive processes is significantly influenced by the aging process. To ensure subject safety and data validity, individuals will be excluded from neuroimaging if they present contraindications for MRI and valid data, such as presence of metal implants or foreign metallic objects, claustrophobia, inability to tolerate the scanning procedures (e.g., lie still on back for 60 minutes), neurological disorders, and medical conditions (e.g., uncontrolled diabetes, stroke, seizures, etc.).

5.1 Inclusion Criteria

- Aged 18-72 years
- Meets current DSM-5 criteria for PTSD (with or without MDD); type of trauma can include interpersonal violence, combat, and sexual assault, etc.

5.2 Exclusion Criteria

- Dissociative PTSD
- Delayed-onset PTSD
- MRI contraindications (e.g. metal in body, inability to be in the scanner – claustrophobia, severe back pain, etc.)
- Serious medical or neurologic conditions (e.g. stroke, seizures)
- Suicide risk
- Psychosis
- Life history of schizophrenia
- Life history of bipolar disorder
- Current substance dependence
- Other factors that preclude safe and meaningful participation in the study, at discretion of the PI and study team

5.3 Lifestyle Considerations

Individuals with a history of drug or alcohol dependence (highly prevalent in PTSD) or pre-existing current treatment with psychotropic medications will not be excluded; however, patients taking these medications must have clearance from psychiatrist.

5.4 Screen Failures

Participants will be considered screen failures if, post-consent, they are deemed ineligible at the initial intake visit or fMRI scan:

- Intake assessment reveals an excluded PTSD sub-type
- Intake assessment reveals a contraindicated psychiatric diagnosis
- Unable to participate in the initial fMRI either because of contraindications or inability to lie still in the scanner or complete the tasks
- Otherwise does not fulfill eligibility criteria

Participants who are found to be screen-failures post-consent will not be enrolled in the clinical trial. However, to improve recruitment and retention of enrolled participants, consented participants who screen-fail due to (a) inability do fMRI scan or (b) who are missing a single PTSD symptom may be allowed to participate in the group psychotherapy and assessment part of the study (whichever their cohort is cluster randomized to, MBCT or MRG). (See section 5.6.1 below).

5.5 LOST-TO-FOLLOW UP

Participants who are lost-to-follow up are those were participating in the study (i.e. enrolled) and are no longer participating in study activities and who do not respond to repeated attempts to contact. In our previous studies, the rates of lost-to-follow up were lower than our non-completion/withdrawal rate as most treatment non-completers were responsive to study team contact and willing to return for outcome assessments.

See Subject Accrual & Recruitment Plan

5.6 STRATEGIES FOR RECRUITMENT AND RETENTION

See Study Accrual & Retention Plan

Patient participants will be recruited from the Ann Arbor/SE Michigan community, which includes three major universities (University of Michigan, Eastern Michigan University, and Wayne State University), and two large VA Hospitals (VA Ann Arbor and VA Detroit). Our extended research group, under the leadership of the Israel Liberzon, MD, who is an Attending Psychiatrist of the VA Mental Health Service, has successfully recruited at least several hundred PTSD patients for a number of fMRI and PET neuroimaging and treatment studies over the past 10 years. In the past 5 years, the PI, Dr. King and colleagues have recruited over 200 persons with PTSD from the community.

The recruitment process consists of several stages for providing information to the potential participant allowing time for the individual to consider involvement. The initial contact is a telephone pre-screening interview during which the study coordinator will administer a brief PTSD screener, share details and parameters of the study, and provide an opportunity for questions. For those are pass the initial screening and express interest in the study, a baseline study visit will be scheduled. The individual will meet with study staff where at which time they will again listen to an explanation of the study, have time to read the consent document and ask questions. During this discussion, the staff member will inquire about the ability of the patient to understand the nature of a research protocol. Signed consent may be provided at this time, or at a subsequent interview if the potential participant would like more time to consider their options. It will be made very clear that the research study offers two 8-week interventions that are experimental manipulations but are not considered a mental health treatment for PTSD. We will request permission to discuss with the participant's PCP and mental health provider(s). We will ask the participant if they would like referral to mental health treatment for PTSD, and if they do, will provide several referrals to local licensed mental health professionals. When the patient signs the consent, the complete assessment process will begin.

Participants who consent to the study but are found to be screen-failures post-consent because they cannot do fMRI scan or are missing a single PTSD symptom will not be formally enrolled in the clinical trial. However, they will be allowed to participate in the group psychotherapy (whichever their cohort is cluster randomized to, MBCT or MRG) and follow-up assessments only. They will sign a separate consent indicating they do not meet the inclusion criteria for the clinical trial / full study, but will be offered the treatment-and-assessment-only parts of the study. The purpose for including screen-fails in the psychotherapy groups is to improve feasibility – i.e. to increase study flow and to avoid unacceptable

wait times for enrolled participants (i.e. who have full PTSD and who have done fMRI). However, to measure and control for group characteristics in multi-level modeling, we will also collect weekly self-report and follow-up assessment on the "treatment-only non-fMRI" participants.

5.6.1 Participant Incentives

Participants will be paid up to $320.00 for completing the study. The payment includes incentive for participation in study procedures and a small travel allowance. Participants will be paid only for the parts of the study completed. Participants who screen-fail fMRI but are allowed to do the treatment will not be paid for the fMRI part of the study.

- $25 per clinical assessment (up to $50)
- $75 per fMRI (up to $150)
- $10 per visit (study assessments and treatment sessions) as travel stipend (up to $120)

6 STUDY INTERVENTIONS

6.1 JUSTIFICATION FOR INTERVENTION

6.1.1 Study of MBCT targets and mechanisms in acute psychiatric disorder (PTSD)

While originally designed as a treatment for depression relapse prevention in remitted patients, there is a growing appreciation that MBCT and related forms of attention training may be a useful approach as an adjunctive treatment or treatment component for acute psychiatric disorders, including hard-to-treat disorders like treatment resistant depression, GAD, anxious depression (chronic comorbid MDD-GAD)[78,79]. Several studies now suggest that mindfulness-based interventions like MBCT are well tolerated and demonstrate efficacy for PTSD in studies of both primarily males with combat trauma[2,24,25,28-32] and primarily females with interpersonal violence and sexual abuse[23,33]. Over the past decade, mindfulness-based approaches have become more common in PTSD treatment; indeed one recent report found that 77% of Department of Veterans Affairs (VA) PTSD specialty programs offered some type of mindfulness training[80]. However, there has been less mechanistic study of effects of MBCT on acute psychiatric disorders. Initial work showing mindfulness may lead to alteration in large scale connectivity networks in PTSD patients[2] (and highly stressed persons[3,81]) is exciting because it suggests the possibility MBCT / other forms of mindfulness training may engage novel treatment targets / novel mechanisms that might combined with other forms of psychotherapy interventions (e.g. exposure, cognitive restructuring, etc.) for persons with acute psychiatric disorders to maximize effects.

6.1.2 Large-scale connectivity networks as targets of MBCT treatment effects

Important findings from translational neuroimaging studies of psychotherapy interventions have identified the importance of alterations in amygdala, insula, and sgACC for example, in treatment of PTSD, MDD, and anxiety disorders (for review[82]) but only recently has research been focused on the effects of psychotherapies or other treatments on the strength of functional connectivities within and between large scale brain networks (reviewed[83,84]). This has mainly focused on seed-based analyses in subcortical regions and role of DMN in depression. Interestingly, in studies of antidepressant medication, while findings of altered connectivity between prefrontal and limbic areas have been reported, most studies have not found strong changes in DMN that correlated with symptom change,

and have not found changes in CEN[83,84]. In contrast, studies of ECT and studies of transcranial stimulation have found increased connectivity in dlPFC[83]; thus findings that MBCT increases PCC-dlPFC connectivity are of considerable interest. Furthermore, unlike most previous studies, we are proposing here to use whole-brain connectomics to test changes in distributed networks. Our co-investigator Dr. Sripada is a leader in development and use of such powerful connectomics methods in studies of psychiatric disorders and now treatment, and our Neuroimaging Methods Core has functional processing streams for the joint ICA connectomics approaches we are proposing here. We are also currently actively developing and testing additional connectomic methods for dynamic connectomics and other applications adding to innovative abilities to interrogate large scale networks in both resting and task-based paradigms.

Based upon previous work by our group and others reviewed above, we propose a mechanistic model in which the syndrome of PTSD is driven in part by hyperconnectivity within the SN (in particular, amygdale-insula), and dysregulated / exaggerated between SN and DMN that is associated with intrusive, automatic distress reactions to both external cues and internal physiological states. Similar dysfunctional vmPFC-insula hyperconnectivity has also been implicated in depression and anxiety[58]. Neuroimaging evidence suggests aberrant functional connectivity in large-scale networks may underlie negativity bias, over-identification and misinterpretation of interoceptive cues, and negative rumination in anxiety, depression, and PTSD.

We propose that MBCT / mindfulness training leads to enhanced connectivity between DMN-CEN and normalized connectivity in DMN-SN that underlie the psychological mechanisms leading to therapeutic change. Several studies find mindfulness training leads to increased connectivity between DMN and CEN / cognitive control networks (e.g. increased PCC-dlPFC, and vmPFC-dlPFC), and decreased DMN-SN connectivity (sgACC-amygdala), both in healthy people and in people with and acute psychiatric disorder (PTSD). These MBCT effects on network connectivity are expressed psychologically as increased decentering (and related psychological constructs of metacognitive awareness, mindfulness, distancing, defusion, etc.), the psychological processes mediating positive mental health outcomes of MBCT. Recent theoretical and empirical work by Fresco et al.[76,85] has further elaborated the construct of decentering into three components: the attentional practice of meta-awareness enables the capacity for dis-identification from internal experience, and reduced reactivity to thought content.

6.2 Study Intervention: MBCT (Mindfulness-Based Cognitive Treatment)

MBCT is a well-documented intervention initially designed for prevention of depression relapse, which has since been successfully adapted to a number of disorders, including depression, GAD, and PTSD. We will use our previously published adaption for PTSD[24]. MBCT includes a number of mindfulness exercises and group discussion; exercises include a) mindful eating (the 'raisin exercise'), b) the 'body-scan' exercise, c) mindful stretching, d) sitting mindfulness of breath exercise and e) the “3-Minute Breathing Space” (a brief mindfulness of breath exercise).

- Group therapy
- 8-weeks
- 2 hours/session
- MBCT exercises at home for ~20-30 minutes on 5 or more days/week
    - Assisted by audio recordings

- Co-led by two trained therapists

6.2.1 MBCT Fidelity

Our consultant Mark Lau, PhD, R. Psych. is an expert trainer in Mindfulness-based Cognitive Therapy (MBCT), certified by the Canadian Association of Cognitive and Behavioural Therapies and the Academy of Cognitive Therapy (ACT).

- To insure adherence and fidelity to the MBCT model, Dr. Lau will consult with therapists via videoconferencing on clinical delivery before and during each MBCT group, including review of session content, and will review video recording of therapists delivering each treatment component.
- MBCT therapists in the study will be licensed mental health professionals with training in PTSD psychotherapy with MBCT Teacher Qualification from UCSD (or equivalent).
- Therapists will have a checklist and materials for each session, and each session will be video recorded. A trained MS-level student will review each session to record that each treatment component was delivered (and start-stop time of each component), and note any divergence from protocol. Relevant portions of videos will be reviewed by therapists before each videoconference with Dr. Lau and will be discussed in consultation.
- Treatment fidelity of therapists will be assessed by delivery of treatment components and therapist competencies, using Mindfulness-Based Interventions-Teaching Assessment Criteria (MBI-TAC)
- Participants will complete treatment logs which will be reviewed at each session

6.3 Study Intervention: Muscle Relaxation Group (MRG)

The control intervention was developed by study consultant, Dr. David Fresco, for use in medical patients with PTSD-material. It is well-balanced with MBCT in terms of time, number of sessions, therapist contact, group support and home practice. The primary difference between MRG and MBCT is the lack of mindfulness instruction and practice in decentering. It is a common active comparator in studies of PTSD, and is a plausible intervention with demonstrated tolerability and efficacy.

Participants will learn progressive muscle relaxation techniques that involve alternately tensing and relaxing various muscle groups to achieve a state of global body relaxation.

- Group sessions
- 8-weeks
- 2 hours/session
- Home exercises comparable duration to MBCT
    - Includes audio recordings to facilitate compliance

6.3.1 MRG Fidelity

- To insure adherence and fidelity to the MRG manual, Dr. Fresco will consult with therapists via videoconferencing on clinical delivery before and during each MRG group.
- MRB therapists in the study will be therapists trained to instruct and guide participants in muscle relaxation exercises.

- Therapists will have a checklist and materials for each session, and each session will be video recorded. A trained MS-level student will review each session to record that treatment content was delivered, and note any divergence from protocol, relevant portions of videos will be reviewed by therapists before each videoconference with Dr. Fresco and will be discussed in consultation.
- Approximately 20% of video recordings will be reviewed by Dr. Fresco or his designee for compliance the intervention and delivery techniques.
- Participants will complete treatment logs that will be reviewed each session.

6.4 Measures to Minimize Bias

The majority of the study team will be blinded until the data are fully collected and the database locked. The table below offers a description of the various study personnel and their blinding status. A NO indicates that a particular stakeholder will not be blinded and a YES indicates that they will be blinded.

Stake holder	Intervention group assignment	Primary Mechanistic Outcome Measure	Clinical/ Functional Outcome Measure
Study Participants	**No**. Participants cannot be blinded to the type of therapy they receive; however, both therapies will be presented as plausible treatments, and cross contamination will be minimized	**Yes**. The mechanistic outcome is a brain connectivity measure; patients will not be appraised of brain scan outcome data.	**Yes**. While PTSD symptoms and pain will be obvious to patients, decentering and physiological measures will not.
Instructors/Practitioners	**No**. The instructors will know which therapy they are delivering	**Yes**. Practitioners will not have access / not be appraised of brain scan data	**Yes**. Practitioners will not have access / not be appraised of outcome data
Outcome Assessors	**Yes**. Assessors will be blinded to group assignment	**Yes**. Assessors will not have access / not be appraised of brain scan data	**Yes**. Assessors will be blinded to group assignment
Data Analysts/Statistician	**Yes**. Analysts will not know group assignment until blind is broken	**Yes**. Analysts will not know group until blind is broken	**Yes**. Analysts will not know group until blind is broken
Principal Investigators	**Yes**. PIs will not know group	**Yes**. PIs will not know group	**Yes**. PIs will not know group

assignment until blind is broken	assignment until blind is broken	assignment until blind is broken

6.5 Concomitant Therapy

Participants will be allowed to continue with their usual and customary PTSD treatments including psychotropic medications under the direction of their psychiatrist. It is expected that these treatments are to remain stable for the duration of an individual's participation.

6.6 Participant Withdrawal from Intervention and Study

Participants may be withdrawn from the treatment or study for a number of different reasons:

- It is not in the best interest of the participant to continue (e.g. worsening of symptoms incompatible with continuing with the treatment or study)
- An individual becomes ineligible (classified as withdrawn if occurs after the initial study visit)
- A change in condition that requires treatment that is not permitted under the protocol
- PI and/or study team can withdraw a participant for not following study instructions or other reasons related to data integrity and safety
- A participant can change their mind about participation

When possible, we will perform study assessments as feasible (i.e. collect self-report measures, but not fMRI), and information related to reason for withdrawal. All data and saliva collected up the point of withdrawal will be retained in the study database to minimize data loss and preserve data integrity.

7 Study Assessments & Procedures

7.1 Psychiatric Diagnostic Status

7.1.1 Mini-International Neuropsychiatric Interview (MINI 7.0.2)

The MINI is a brief structured diagnostic interview instrument to assess for major psychiatric disorders that can be administered in ~15 minutes.

7.1.2 Clinician-administered PTSD Scale (CAPS-5)

The CAPS-5 is a 30-item clinician-administered PTSD assessment. It is used to make both current and lifetime diagnoses of PTSD as well assess recent symptoms. The full interview takes ~45-60 minutes to complete.

7.1.3 PTSD Checklist (PCL-5)

The PCL-5 is a 20-item self-report instrument that assesses DSM-5 PTSD symptoms. It is used to monitoring symptom change and as a screening tool.

7.1.4 Hamilton Depression Scale (HAM-D)

The HAM-D is a 21-item clinician-administered instrument for determining depression severity before, during and after treatment. It takes approximately 15-20 minutes to administer and score (only the first 17 items are used to calculate the score)

7.1.5. Matrix reasoning

This is a sub-scale of the Wechsler Adult Intelligence Scale-IV (WAIS-IV). This is an untimed, nonverbal reasoning task in which individuals are asked to identify patterns in designs. It usually takes between 8-15 min to complete. This subtest measures: non-verbal reasoning skills, broad visual intelligence, and perceptual organization skills related to fluid intelligence (gF). This measure will be used as a cross-validation for the fMRI connectivity analyses.

7.2 Quality of Life and Outcome Assessments

7.2.1 Beck Depression Inventory (BDI-II)

The BDI-II is a 21-item self-report measure of depressive symptoms. Scores range from 0-63 with higher numbers suggesting more severe depression.

7.2.2 Experiences Questionnaire – Decentering Factor (EQ)

The EQ is an 11-item self-report measure that captures both decentering and rumination. Scores range from 11-55 with higher values suggesting greater decentering.

7.2.3 Acceptance and Action Questionnaire (AAQ)

The AAQ is a 9-item self-report measure of experiential avoidance and psychological inflexibility. Higher scores suggest greater avoidance and immobility while lower scores reflect greater acceptance and action.

7.2.4 Multifacet Mindfulness Questionnaire (MMQ-15)

The MMQ-15 is a 15-item self-report measure of trait-like tendencies to mindful in everyday life. It includes the facets of describing, acting with awareness, nonjudging, and nonreactivity. Scores for each facet range from 3-15.

7.2.5 Emotional Regulation Questionnaire (ERQ)

The ERQ is a 10-item self-report measure of the tendency to regulate emotions in two different ways: cognitive reappraisal and expressive suppression. Each facet is scored separately.

7.2.6 Response Styles Questionnaire, Ruminative Response Subscale (RSQ-RRS)

The RSQ-RRS is an 11-item self-report measure of ruminative tendencies in response to negative emotion. Higher scores suggestion greater rumination.

7.2.7 Brief Pain Inventory (BPI)

The BPI is a self-report measure of pain intensity (3 items) and pain interference (9 items) with everyday activities. Higher scores reflect greater intensity and more interference.

7.2.8 Life Events Checklist (LEC)

The LEC is a self-report measure designed to screen for potentially traumatic events in an individual's lifetime. It includes 16 events known to potentially contribute to the development of PTSD or ongoing distress, and includes an additional item for "other" events no otherwise captured by the list.

7.2.9 Childhood Trauma Questionnaire (CTQ)

The CTQ is a self-report measured designed to capture potentially traumatic experiences that occurred in childhood and in the teenage years.

7.2.10 Self-Compassion Scale

Short form (12-item) self-report measure of self-compassion. It includes 4 items for self-kindnes vs self-criticism, 4 items for mindfulness, 4 items for recognizing common humanity aspects of one's actions.

7.2.11 Posttraumatic Cognitions Inventory (PTCI-9)

The PTCI-9 is a brief form 9-item self-report instrument that assesses cognitions associated with PTSD risk, including 3 items each related to negative self views, dangerous world, and self-blame.

7.3 RESEARCH PROCEDURES

7.3.1 Functional Magnetic Resonance Imaging (fMRI)

Neural mechanisms (BOLD – blood oxygen-level-dependent imaging – activity) will be assessed using two paradigms that will be counter-balanced to control for order effects:

Resting Connectivity – Participants are asked to "remain still, keep your eyes open and on the fixation mark, let your mind wander freely and do not fall asleep." This scan lasts approximately 10 minutes.

Resting Connectivity – Participants are asked to "remain still, keep your eyes open and on the fixation mark, and do not fall asleep. Please bring your attention to the sounds in the scanner and the feelings and sensations in your body. When you notice your mind wandering, please bring your attention back to the sensations in your body". This scan lasts approximately 10 minutes.

Context Separation and Completion Task: To assess pattern separation and pattern completion abilities specific to complex contextual scenes, participants will view two target images of rooms with different configurations of furniture ("room A" and "room B"), and then shown a series of images of rooms with various configurations of furniture and asked to choose whether it is most similar to "room A" or "room B". These mages will have items replaced or moved to create varying degrees of similarity to the original scenes A or B. This will allow us to determine each subject's threshold for pattern completion (categorizing the previously viewed image correctly), pattern separation (categorizing the new image as never seen before) and overgeneralization (incorrect categorization). This task will take approx. 15 mins to complete. MRI will be used to examine hippocampal and PFC activation related to context discrimination abilities.

Self-related Processing Task[5] – This task consists of viewing eight sets of words, each containing six personality-trait adjectives (e.g. lively, productive, indecisive, clumsy). Participants will view the sets of words. Each word in the set will be displayed for 4 seconds each (with a 2 second delay between words), for a total of 36 seconds per set. Before the display of each word "set" there will be an instructions displayed, saying to perform either the "Narrative" or "Experiential" task. The participant

will be asked to perform one of these two 'tasks' while viewing the words. "Narrative" consists of viewing each word and thinking about what the trait word means to the participant, whether it describes the participant, and allowing oneself to become "caught up in a given train of thought". "Experiential Focus" will involve engaging present-centered self-reference, sensing what is occurring in one's thoughts, feelings and body state, without purpose or goal, other than noticing how things are from one moment to the next. Each participant will complete 2 runs in the scanner (each run will be two repetitions of each condition, so the total task will consist of a total of 8 lists, or ~8 min in length. Participants will be trained in how to engage in these different forms of self-focus before the scan (~10 min), and after the scan will be asked to recall which words they remember.

7.3.2 Pregnancy test

Each female participant of child-bearing age will take a urine (dipstick) pregnancy before each scan. Individuals testing positive not go through the scan.

7.3.3 Saliva specimen collection for adrenergic and inflammatory biomarkers

Participants will provide saliva samples by passive drool (spitting into plastic tubes) at 4 points during the MRI scan – upon arrival, immediately before entering and after exiting the scanner, and before departing the MRI facility.

7.3.4 Measures of emotional engagement. In the assessment session before the CAPS interview, patients be administered the "standardized trauma interview"[118] (STI, a very common interview that is in first session of PE) and will be video-recorded and heart rate responses (ECG) and skin conductance (SCR) measures taken using a mobile (tablet controlled) psychophysiology system as previous described[119]. The videos will be stored and later scored at VA Ann Arbor using the Levels of Engagement Scale (LES) by raters on three dimensions of a) willingness, b) psychological contact with trauma memories, and c) emotional responsiveness. Heart rate responses (HRR) and skin conductance responses (SCR) to the trauma memory will be calculated as previously reported[119].

7.4 Safety Assessments

See Data & Safety Monitoring Plan

7.4.1 MRI screening

Individuals are pre-screened by the study team for MRI contraindications, and then the technicians screen prior to each scan

7.4.2 PHQ-9

The PHQ-9 is a brief self-report assessment that measures depression symptoms and suicidal ideation. It will be scored in real-time so that any indication of suicide risk can be addressed immediately.

7.4.3 Columbia Suicide Severity Ratings Scale (C-SSRS)

The C-SSRS is 6-item assessment tool that evaluates suicidal ideation and behavior. It will only be administered if indicated by participants' responses on the PHQ-9.

7.4.4 Clinical Global Impressions Scale (CGI)

The CGI has two components – severity ("Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" scored on a 7-point scale ranging from normal to among the most extremely ill patients) and Improvement ("Compared to the patient's condition at admission to the project, this patient's condition is…" scored on a 7-point scale ranging from very much improved to very much worse.

7.4.5 PCL-5

The PCL-5 is a 20-item self-report instrument that assesses DSM-5 PTSD symptoms. It is used to monitoring symptom change and as a screening tool (see Section 6.7.3).

7.5 Adverse Events & Serious Adverse Events

See Data & Safety Monitoring Plan

7.5.1 Suicidal Ideation

Study participants are people with current PTSD with or without co-morbid with major depression. Clinical epidemiology estimates the annual incidence of suicidal ideation in the US general population to be ~5% with higher rates observed in both PTSD and depressed patients. At baseline and throughout the study (assessments, scans, and therapy sessions), participants will complete a number of survey measures to assess clinical status and potential suicidal ideation.

- The PHQ-9 will be scored in real-time so that any indication of suicide risk can be dealt with immediately.
- If suicidal ideation or behavior is indicated at any time in conjunction with the study, UM study personnel will immediately take measures to assess the severity of the risk, and apply safety measures as appropriate and clinically indicated.
- Suicide risk severity will be assessed using the Columbia Suicide Severity Rating Scale, considered a "gold standard" for suicide risk assessment.

If suicide risk is assessed to be moderate or high with potential for imminent danger, the study therapists / other study team will work with the participant to ensure clinically appropriate care, including contact with and possible transportation by ambulance to University of Michigan (UM) Psychiatric Emergency Services (PES).

- The PI and the UM medical monitor (respectively) will be notified immediately and will be available to assist with assessment and coordination of safety measures and clinical care.
- The PI and all participating University of Michigan study personnel carry pagers and can be reached at any time through PES, which is open 24 hours a day, 365 days per year. Our project team is comprised of four Board Certified Psychiatrists and two Licensed Psychologists, all of whom will be available to study psychotherapists (who are also licensed mental health providers) and other study staff (e.g. study coordinator, independent assessors) should concerns arise to determine the need for a higher level of care and support the study staff and study psychotherapists in making make appropriate recommendations and referrals.

- This will also be reported to IRB as an AE or a SAE, depending upon how the situation is resolved.

7.5.2 Clinical Worsening

While the majority of PTSD patients show improvement and decrease in symptoms in response to MBCT and MRT, some patients do not improve, and a small proportion experience clinical worsening and increased psychiatric symptoms during treatment. Clinical worsening could occur due to treatment-specific factors as well as factors not related to the treatments per se (e.g. experience of stressful life events during the study).

Clinical worsening will be defined as clinically significant increase in psychiatric symptoms (based on current accepted professional standards) assessed from self-report measures used in the study (PCL-5 or PHQ-9) or worsening on clinician-rated Clinical Global Clinical Impression (CGI, e.g. rating of 6-much worse or 5-very much worse) that occurs over two consecutive weeks. Intermittent worsening of symptoms, as well as worsening that is below current accepted professional thresholds of "clinically significant" will also be reported to the PI and Co-Is at weekly Team Meeting, and on case-by-case basis, could also trigger report to medical monitor and clinical review to determine whether alternate or higher-level psychiatric care is necessary.

- Psychiatric symptoms will be monitored weekly by study therapists
- Clinically significant worsening of symptoms whether or not they are deemed related to the study treatments will be reported to both PI and medical monitor within 24 hours, and will trigger a clinical review to determine whether an alternate or higher level of psychiatric care is necessary for the patient.
    - This may include further psychiatric evaluation of the participant by the PI and/or study medical monitor
    - Such occurrences will be reported to IRB as AE or ORIO, and the participant may be required to exit the study if alternative care is found to be necessary. Referrals for alternate psychiatric care will be made by the medical monitor or their designee

7.5.3 Assessment and management of participants with PTSD who have panic symptoms or an exacerbation of PTSD symptoms when they are undergoing an MRI scan or are in the MRI center.

While the vast majority of PTSD patients we have scanned over the past 12 years have not had panic reactions or exacerbation of PTSD symptoms in the MRI scanner or center, such situations have occurred and is a possible occurrence. In order to minimize the risk of an anxiety reaction/panic attacks induced by confinement in the scanner, the subjects are allowed to communicate with the machine operator via an intercom and may trigger an audible alarm at any time. Before the subject is placed in the magnet, he or she is reminded that they are free to stop the study at any time if they become uncomfortable. In the event of an adverse event due to anxiety reaction/panic attacks leading to participant triggering the alarm in the MRI, or communicating that they wish to stop, or if the study research personnel determines that a participant is having an anxiety reaction or panic attack at any time in the MRI facility, the experiment would be immediately terminated and the participant would be immediately removed from the scanner. Research personnel will be trained to monitor for this and notify the PI immediately, and will take appropriate acute counseling measures. The PI Dr King is a licensed psychologist at Michigan Medicine Outpatient Psychiatry Anxiety Disorders Clinic specializing in

PTSD and anxiety, co-Is Dr Favorite and Dr Fresco are licensed psychologists specializing in PTSD and anxiety, co-Is Dr Abelson, Dr Muzik, and Dr Sripada are all board-certified psychiatrists at Michigan Medicine specializing in Anxiety and/or PTSD. The PI and/or clinical co-Is will be notified immediately by pager or cellphone contact, and will provide immediate onsite counseling and referral to an appropriate psychological or psychiatric facility (e.g. Michigan Medicine Psychiatry or Psychological Clinic) in case of crisis or need for debriefing that day, or if they want referral after the scan. In addition, even if the participant does not receive a referral for mental health treatment, follow-up telephone calls would be made within 1-3 days of an episode to confirm the transient nature of their reaction.

- Psychiatric symptoms will be monitored at the MRI by study team
- Clinically significant anxiety reaction, panic attack, or exacerbation of PTSD symptoms at the MRI center, whether or not they are deemed related to the study treatments, will be reported to both PI and medical monitor within 24 hours, and will trigger a clinical review to determine whether an alternate or higher level of psychiatric care is necessary for the patient.
    - This may include further psychiatric evaluation of the participant by the PI and/or study medical monitor
    - Such occurrences will be reported to IRB as AE or ORIO, and the participant may be required to exit the study if alternative care is found to be necessary. Referrals for alternate psychiatric care will be made by the medical monitor or their designee

7.6 Unanticipated Problems

See Data & Safety Monitoring Plan

8 Statistical Considerations

8.1 Go/No Go Criteria – Primary mechanistic outcome

Our primary hypothesis that dictates GO to R33 is that MBCT will lead to specific changes in specific circuits within DMN and CEN. Specifically, our R61 Go/No-Go criteria is **increased functional connectivity between dlPFC and PCC** in the MBCT condition compared to the MRG active control reflected in a clear effect size (d>0.60). This will be tested in analyses of resting state functional connectivity (using a PCC-seed) using group contrast and repeated measures ANOVA (RM-ANOVA) approach in spm: specifically testing for between-group difference in PCC-dlPFC rsFC post-intervention, and/or a Group x Time spreading interaction between treatment group (MBCT vs MRG) and Time (pre vs post treatment)

To test PCC-dlPFC rsFC, we will use a search region ROI mask using the Wake Forest University PickAtlas Automatic Anatomical Labeling atlas consisting of the left and right middle frontal cortex (based upon findings of Brewer et al., 2011, Creswell, et al., 2016; King et al., 2016). We must find a cluster of rsFC in dlPFC region defined above that is statistically significant in a pre-post between-group comparison (MBCT > MRG).

8.2 Secondary Mechanistic Outcome

We hypothesize we will also see change in our secondary brain mechanism (decreased Insula-PCC rsFC) that is related to decrease in PTSD symptoms following both interventions. We hypothesize that this is a treatment target common to MBCT and other approaches, whereas increased PCC-dlPFC is specific to MBCT. We further hypothesize that increased PCC-dlPFC rsFC from MBCT will drive increased engagement in naturalistic vivo exposures and thereby decrease PTSD symptoms and thereby Ins-PCC rsFC.

9 Operational Considerations

9.1 Informed Consent Process

The recruitment through enrollment process consists of several stages for providing information to the potential participant. At the initial study visit the study staff will meet with individuals to explain the study again and to review the consent document. The proceeding discussion will focus on the voluntary nature of the research study, that it is distinct from clinical care or therapy for PTSD, a review of study procedures and participant responsibilities, and risks-benefits of participation. The study staff will inquire about the ability of the potential participation to understand the nature of the protocol. Documented informed consent may occur at this time, or at a subsequent time if the potential participant would like more time to consider their decision.

The consent process will take place in private space.

9.2 Confidentiality and Privacy

All encounters with potential and enrolled participants will take place in private space (e.g. exam room, research room, office, etc.). Study staff will be trained in Michigan Medicine privacy practices and dealing with confidential or sensitive information. Therapy sessions will be closed, and participants instructed to respect one another's privacy.

Data elements and saliva samples will be coded with identifiers stored in a password-protected HIPAA-compliant database. All research data and samples will be under the purview of the PI and access will be restricted based on job role.

9.2.1 Source Document and Data Management

See Data & Safety Monitoring Plan

9.2.2 Data Retention for Study Record Keeping

All study identifiable data and information from this study will be retained for the duration of this study and at least through the accrual period of the subsequent R33 portion of the funding mechanism. Study records will be coded, and the link to identifiers stored in the HIPAA-compliant study database. Access will be under the purview of the PI and restricted to authorized study staff. We are retaining these data to prevent co-enrollment in both the R61 and R33 and preserve data integrity.

- Pre-screening information will not be retained for those individuals deemed ineligible or otherwise unsuitable for the study. The records will be destroyed after the interview.

The de-identified study database will be archived and stored on Michigan Medicine servers. Hard copies of identifiable study records (e.g. consent document) will be retained for at least 3 years beyond submission of the final progress report or publication of the primary manuscript, whichever is later. Health-related data will be retained for at least 7 years beyond submission of the final progress report.

- Recordings will be stored in the study database and be used for ongoing therapist training.

9.2.3 Future Use of Specimens and Data

Identified data will be retained for possible future research use for a minimum of 2 years beyond the completion of the current study to allow for potential long-term follow-up assessments. We will not undertake these assessments, or other future unspecified research without additional IRBMED-approval.

- Identified data will be stored in a HIPAA-compliant database on Michigan Medicine servers
- Access to the database will be under the PI's purview and access-restricted
- Datasets shared with collaborators will stripped of identifiers and date-shifted

9.3 Data Handling and Record Keeping

See Data & Safety Monitoring Plan

9.4 Data Sharing

Data and materials generated under this project will be administered in accordance with NIH Sharing policies, including NIH Policy on Dissemination of NIH-Funded Clinical Trial Information (8/2016), and the NIH Grants Policy Statement (Availability of Research Results) (11/2015) - Section of the NIH Grants Policy Statement which discusses the availability of research results developed with NIH funding, including publications, data, unique research resources, and intellectual property (inventions and patents.

Depending on such NIH policies, data and materials generated by this project may be transferred to others under the terms of a data or material transfer agreement. Access to databases generated by the project will be available for educational, research and non-profit purposes.

9.4.1 Publication of Results

Publication of data will occur during or shortly after the completion of the project, consistent with normal scientific practices.

9.4.2 fMRI Data

We plan to make available data from fMRI scans from human subjects initially to collaborators for independent replication / data pooling. We also plan to make the de-identified brain scans available to the broad scientific community in public databases once the main findings from the finalized research

dataset have been accepted for publication. However, additional redaction steps may need to be made to brain scans to ensure subject confidentiality / inability to identify individuals from brain scans.

9.4.3 De-identified Research Data

Completely de-identified research data (redacted according to NIH practice to prevent disclosure of personal identifiers) which documents the research findings will be made available after the main findings from the finalized research dataset have been accepted for publication.

9.4.4 Genome Wide Association Studies

Not applicable

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National Center for Complementary and Integrative Health

Tool Revision History:

Version		
Number	**Date**	**Summary of Revisions Made:**
1.0	**07Sept2018**	**First approved version**

Data and Safety Monitoring Plan (DSMP)

Independent Monitoring Committee

Protocol for Neural Mechanisms of Mindfulness-based Cognitive Therapy (MBCT) for Posttraumatic Stress Disorder (PTSD)

Name of Sponsor:	National Center for Complementary and Integrative Health
Grant Number:	1 R61 AT009867-01
Version Date:	15 September 2018
Version Number:	1.0

DATA SAFETY MONITORING PLAN (DSMP)

1. STUDY OVERVIEW

1.1 Purpose of Study

The purpose of the proposed research is to generate new knowledge about changes in brain activity and connectivity associated with mindfulness-based Cognitive Therapy (MBCT) for posttraumatic stress disorder (PTSD), and how these are related to the therapeutic mechanism of action of MBCT. Understanding the mechanisms of action of MBCT, and whether they are different from other forms of therapy, such as exposure, will be crucial for designing more efficient and effective PTSD interventions.

The R61 phase is designed to identify specific MBCT-linked changes in brain connectivity. We hypothesize increased connectivity between the dorsolateral prefrontal cortex (dlPFC), involved in attentional control, and the posterior cingulate cortex (PCC), involved in mind-wandering and self-referential processing, as a putative treatment target. We will compare the effects of MBCT to a well-matched control intervention, group muscular relaxation therapy (MRG).

The R33 phase is designed to optimize effects of MBCT and this dlPFC-PCC target by combining MBCT with another non-trauma-focused group intervention, In vivo Exposure. We will compare MBCT+In vivo Exposure vs MRG+In vivo Exposure and perform formal testing of mediation by targets of improvements in psychological health, PTSD symptoms, and additional functional outcomes. We will test for treatment group differences in network target engagement and its mediation of changes in decentering, PTSD symptoms, acceptance, stress reactivity, functionality, and quality of life. The improved understanding of such neural mechanisms and their relationships to psychological and physiological functioning is expected to direct development of targeted PTSD treatments, with the promise to ultimately improve social functioning and quality of life of people afflicted by PTSD.

1.2 Adherence Statement

The Data Safety Monitoring Plan (DSMP) outlined below will adhere to the protocol approved by the University of Michigan and VA Ann Arbor IRBs.

2 PROTOCOL AMENDMENTS

All protocol amendments, other than minor administrative changes as defined by the NCCIH Guidance on Changes in Clinical Studies in Active Awards will be submitted in a prospective manner to NCCIH except when necessary to protect the safety, rights, or welfare of subjects. Prior to submission to NCCIH the proposed changes will be reviewed and approved by the Independent Monitor(s). IRB-approval will not be sought until after NCCIH approval of the protocol amendment has been obtained.

3 MULTI-SITE STUDIES

Not applicable, though we will recruit throughout the Ann Arbor / Detroit area, this will be a single “site” and institution (University of Michigan), with a single study coordination and data management team.

4 CONFIDENTIALITY

4.1 Protection of Subject Privacy

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

4.2 Confidentiality During Adverse Event (AE) Reporting

AE reports and annual summaries will not include subject or group-identifiable material. Each report will only include the identification code.

5 EXPECTED RISKS

Expected risks to the subject are as follows:

- Clinical assessment. There is a risk of loss of confidentiality and/or feeling uncomfortable about sensitive information such as psychiatric history. Such information could be inadvertently and inappropriately shared with third parties. We will take extensive steps to safeguard confidentiality, and thus this risk is considered to be unexpected and extremely infrequent.

- Magnetic resonance imaging. The presence of metal implants or foreign metallic objects could cause serious injury. However, our scanning facility take measures to reduce risk including redundant safety monitoring and this expected risk is highly infrequent. The noise of the scanner may be harmful to hearing. Subjects may experience discomfort due to lying still during the 75-minute scan, or experience an anxiety reaction due to confinement in the scanner. They may experience peripheral nerve stimulation (described as a light touching sensation on the skin surface) which may be uncomfortable but is not harmful. Imaging may reveal an abnormality that is already in the brain, such as a cyst of tumor. Many such incidental findings are not clinically significant, but the subject may want to investigate them further. Given the precautions described below (Protection Against Risk), we believe that the frequency and thus likelihood of harm from these potential risks is very low. The local IRB has determined studies we have conducted that are similar to the present study as presenting “no more than minimal risk,” meaning that the risks are comparable to those ordinarily encountered in daily life or during routine physical or psychological examinations.

- Inserting a needle for blood sampling and placing a venous catheter for injection or infusion can be associated with some discomfort and bruising, and very rarely with inflammation and infection of the arm veins.

  These risks are considered to be minimal and are addressed in the protocol and consent form.

- Psychiatric disorders like PTSD and their treatment are associated with risk, including distress and suicidal ideation and behavior. Therefore all study participants will be monitored at frequent intervals (weekly) during this part of the study and followed for a sufficient period of time (1 month) after the procedure to ensure stabilization.

  Participants who meet criteria for psychiatric disorders at the conclusion of the study but are not in current treatment will be offered referral to appropriate treatment in the community.

6 ADVERSE EVENT/ UNANTICIPATED PROBLEMS

6.1 Definitions

6.1.1 *Adverse Event (AE)*

An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment, or any combination of these regardless of relationship to participation in the study.

6.1.2 *Unanticipated Problems (UP)*

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.1.3 *Serious Adverse Event (SAE)*

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical

judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.2 Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the study. The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

6.2.1 ***Procedures for participants who report suicidal ideation or experience clinical worsening during study participation***

Psychiatric risk including suicide risk will be assessed at each meeting of study staff with participants (recruitment / consent, assessments, fMRI scans, and therapy groups), and measures to protect participants will be in place throughout the study. Participants will have contact with psychotherapists (who are licensed mental health providers) on a weekly basis while they are engaged in the therapy groups, and will also complete brief symptom self-report measures including assessment of suicidal ideation as part of weekly therapy. The therapists and assessors will assess acute risk factors and current psychiatric state and progress for each participant each week, based upon self-report measures as well as clinical observation.

6.2.2. ***Suicidal Ideation:***

Study participants are people with current PTSD, which is often co-morbid with major depression. Clinical epidemiology estimates the annual incidence of suicidal ideation in the US general population to be ~5%, and both PTSD and depression are associated with considerably higher rates of suicidal ideation. Since suicidal ideation is associated with increased risk for suicidal behaviors, we will take appropriate safety measures to insure safety in study participants who are assessed to have suicidal ideation. At baseline and throughout the study (assessments, scans, and therapy sessions), participants will complete a number of survey measures. Measures that provide indication of risk for suicide (PHQ-9) will be collected and scored immediately after participants complete them so that any indication of risk for suicide can be responded to immediately. If suicidal ideation or behavior is indicated at any time in conjunction with the study, UM study personnel will immediately take measures to assess the severity of the risk, and apply safety measures as appropriate and clinically indicated. Suicide risk severity will be assessed using the Columbia Suicide Severity Rating Scale, considered a “gold standard” for suicide risk assessment. If suicide risk is assessed to be moderate or high with potential for imminent danger, the study therapists / other study team will work with the participant to ensure clinically appropriate care, including contact with and possible transportation by ambulance to University of Michigan (UM) Psychiatric Emergency Services (PES), for participants recruited from the community and engaging in treatment through the study at UM. For participants recruited from the VA Ann Arbor

and engaging in treatment through the study at VA Ann Arbor, clinically appropriate care will include contact with and personal escort to the VA Ann Arbor Emergency Service, located onsite at the VA Ann Arbor Medical Center. The PI and the UM or VA medical monitor (respectively) will be notified immediately and will be available to assist with assessment and coordination of safety measures and clinical care. This will also be reported to IRB as an Adverse Event or a Serious Adverse Event, depending upon how the situation is resolved. The PI and all participating University of Michigan study personnel carry pagers and can be reached at any time through Psychiatric Emergency Services, which is open 24 hours a day, 365 days per year. Our project team is comprised of four Board Certified Psychiatrists and two Licensed Psychologists, all of whom will be available to study psychotherapists (who are also licensed mental health providers) and other study staff (e.g. study coordinator, independent assessors) should concerns arise to determine the need for a higher level of care and support the study staff and study psychotherapists in making make appropriate recommendations and referrals.

6.2.3. ***Participants who experience clinical worsening during study participation***

While the majority of PTSD patients show improvement and decrease in symptoms in response to both trauma-focused and non-trauma-focused psychotherapy (such as being used in this study), some patients do not improve, and a small proportion experience clinical worsening and increased psychiatric symptoms during treatment. Clinical worsening could occur due to treatment-specific factors as well as factors not related to the treatments per se (e.g. experience of stressful life events during the study). Psychiatric symptoms will be monitored by study therapists weekly by clinical observation of patients, and by symptom self-report measures. Clinically significant worsening of symptoms assessed during the study treatments, whether or not they are deemed to be related to the study treatments, will be reported to both PI and medical monitor within 24 hours and will trigger a clinical review to determine whether an alternate or higher level of psychiatric care is necessary for the patient. This may include further psychiatric evaluation of the participant by the medical monitor or a clinician delegated by the medical monitor who wil report back to the medical monitor. Such occurences will also be reported to IRB as an Adverse Event (AE) or Other Reportable Information or Occurrence (ORIO), and the participant may be required to exit the study if alternative care is found to be necessary by the medical monitor. If necessary, referrals for alternate psychiatric care will be made by medical monitor or their designate. “Clinical worsening” will be defined as clinically significant increase in psychiatric symptoms (based on current accepted professional standards) assessed from self-report measures used in the study (PCL-5 or PHQ-9) or worsening on clinician-rated Clinical Global Clinical Impression (CGI, e.g. rating of 6-much worse or 5-very much worse) that occurs over two consecutive weeks. Intermittent worsening of symptoms, as well as worsening that is below current accepted professional thresholds of “clinically significant” will also be reported to the PI and Co-Is at weekly Team Meeting, and on case-by-case basis, could also trigger report to medical monitor and clinical review to determine whether alternate or higher-level psychiatric care is necessary.

6.3 Characteristics of an Adverse Event

6.3.1 *Relationship to Study Intervention*

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

6.3.2 *Expectedness of SAEs*

The Study PI and Independent Monitoring Committee will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

6.3.3 *Severity of Event*

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

6.4 Reporting Procedures

6.4.1 *Unanticipated Problem Reporting*

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- A detailed description of the adverse event, incident, experience, or outcome;
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 7 days of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 14 days of the investigator becoming aware of the problem.

All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

6.4.2 *Adverse Event Reporting of Non-IND Studies*

This psychotherapy study does not include any medications or INDs. SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Safety Monitor(s), IRB, and NCCIH in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer, and Independent Safety Monitor(s) within 3 days of the investigator becoming aware of the event. Other serious and unexpected AEs related to the intervention will be reported within 7 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Safety Monitor(s), IRB, and other oversight organizations in accordance with their requirements. and will be reported to NCCIH on an annual basis.
- All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the Independent Monitors. The Independent Safety Monitor(s) Report will state that all AEs have been reviewed.

6.4.3 *Reporting of Pregnancy*

Because this study involves fMRI brain scanning, pregnant women will be excluded. Pregnancy tests will be completed at time of recruitment and before scans. Currently very similar interventions (Mindful Yoga for High Risk Pregnant Women) is being offered by our collaborator Dr Maria Muzik, and is found to be well tolerated and lead to improvements in psychiatric symptoms. Women who are pregnant will be referred to similar treatment options if interested.

6.5 Halting Rules

Serious, unexpected, and related AEs would prompt temporary suspension of enrollment and/or study interventions until a complete safety review is convened (either routine or ad hoc). The objective of the safety review is to determine whether the study (or intervention for an individual or study cohort) should continue per protocol, proceed with enhanced monitoring, be further investigated, be discontinued, or be modified and then proceed. Suspension of enrollment (for a particular group, a particular study site or for the entire study) is a potential outcome of a safety review.

Subsequent review of serious, unexpected, and related AEs by the Medical Monitor, DSMB/ Independent Safety Monitor(s), IRB, or relevant local regulatory authorities may also result in suspension of further study interventions/administration of study product at a site. The FDA and study sponsor(s) retain the authority to suspend additional enrollment and study interventions/administration of study product for the entire study, as applicable. Findings that might trigger a safety review are the number of overall SAEs (e.g. increases in suicidal ideation or behaviors), the number of occurrences of a particular type of SAE, severe AEs, or increased frequency of events.

7 QUALITY CONTROL AND QUALITY ASSURANCE

Quality Management activities by the study team will include establishing and ensuring the quality of processes, data, and documentation associated with clinical research activities. This psychotherapy study will have standard operating procedures (SOPs) that are briefly described here:

- Staff training methods - all study staff will be trained annually good clinical practice, research ethics, data security, etc using the computerized CITI training system and The University of Michigan human subjects training system. Training will be tracked for all study staff by training certificates which will be in the study regulatory binder.
- Data will be evaluated for compliance with the protocol and for accuracy in relation to source documents by the study coordinator and data manager, deviations will be reported to study PI on weekly basis. Data documents to be reviewed include data sheets, questionnaires, and specimen tracking logs.
- In addition, we will conduct quality / fidelity assurance for our Mindfulness-based Cognitive Therapy (MBCT) intervention as well as fidelity measurement of therapist competencies. Our consultant Mark Lau, PhD, R. Psych. is an expert trainer in MBCT, certified by the Canadian Association of Cognitive and Behavioural Therapies and the Academy of Cognitive Therapy (ACT). To insure adherence and fidelity to the MBCT model, Dr Lau will consult with therapists via videoconferencing on clinical delivery before and during each MBCT group, including review of session content, and will review video recording of therapists delivering each treatment component. Therapists will have a checklist and materials for each session, and each session will be videorecorded. A trained MS-level student will review each session to record that each treatment component was delivered (and start-stop time of each component) and note any divergence from protocol, relevant portions of videos will be reviewed by therapists before each videoconference with Dr Lau and will be discussed in consultation. Treatment fidelity of therapists will be assessed by delivery of treatment components and therapist competencies, using Mindfulness-Based Interventions-Teaching Assessment Criteria (MBI-TAC) and Mindfulness-based Cognitive Therapy Adherence Scale (MBCT-AS)..
- The PI will be responsible for addressing quality assurance issues (correcting procedures that are not in compliance with protocol) and quality control issues (correcting errors in data entry). A statement reflecting the results of the ongoing data review will be incorporated into the Annual Report for the Independent Safety Monitor(s).
- Frequency of QA/QC checks is shown in Table A below.

7.1 Subject Accrual and Compliance

7.1.1 *Measurement and Reporting of Subject Accrual*

Review of the rate of subject accrual and compliance with inclusion/exclusion criteria will occur monthly during the recruitment phase to ensure that a sufficient number of participants are being enrolled, in keeping with proposed recruitment projections, and that they meet eligibility criteria and fulfill the targeted ethnic diversity goals outlined in the grant proposal (Targeted/Planned Enrollment Table).The study site will submit accrual reports to NCCIH at least every 4 months.

7.1.2 *Measurement and Reporting of Participant Adherence to Treatment Protocol*

Data on adherence to the treatment protocol will be collected weekly by research staff and reviewed monthly by the PI/Internal QA Reviewer. Adherence of participants will be evaluated by attendance of at least 5 of 8 group sessions, and turning in "homework" practice logs indicating engaging in mindfulness or in vivo exposure at least once a week. Available data on the use of MBCT in PTSD suggests an overall compliance rate of ~80% completion rate. If adherence falls below the suggested rate, which might inhibit the ability of the study to test its primary hypotheses, the Internal QA Reviewer will suggest a conference call for study investigators to discuss methods for improving adherence.

7.2 Justification of Sample Size

R61 Phase - sample size justification and power analyses: we are proposing to study a total of N=60 participants with PTSD in a two-group, longitudinal "pre-post" design, based upon our preliminary data and feasibility within the mechanism. We will compare MBCT (N=30, N~22 completers) with Muscular Relaxation Group (MRG, N=30, N~22 completers). Our pilot data using seed-based DMN rsFC pre-post MBCT compared BOLD activity of the two groups at the post-treatment time-point extracted from a dlPFC ROI centered on the group x time interaction (a conservative comparison), and found difference statistic of ($t=3.29$, $p<.005$), from which we estimate a small N-adjusted effect size (Hedge's g) of 1.44. In our revised design, we will randomize N=30 to MBCT and N=30 to PE-in vivo to obtain N~22 completers in each group (assuming 25% drop rate), Based upon pilot effect size, power estimates (using G*Power) find sufficient power to detect effect sizes to d=0.6 difference in PCC-dlPFC with beta >80% in between-group two-sample t-tests at the post-treatment time-point.

R33 Phase - sample size justification and power analyses: The R33 has 3 scans: (1) at intake (2) after MBCT or MRG, and (3) after PE In vivo. We hypothesize MBCT will show greater increase in dlPFC-PCC connectivity than MRG (between-groups comparison of scan 2). We are proposing increased dlPFC-PCC as our primary mechanism unique to MBCT, that will not be induced by Relaxation (as recently also reported by Creswell et al., 2016). We also hypothesize that MBCT+PE will show greater increase in dlPFC-PCC, greater decrease in Insula-PCC connectivity at Scan 3, and greater improvement in PTSD and functional outcomes than MRG-PE. As stated above, we hypothesize that MBCT will lead to greater capacity for successful engagement in subsequent in vivo exposure, and thus will lead to additive effects with in vivo exposure, as two therapeutic mechanisms will be engaged (increased dlPFC-PCC from MBCT, and decreased Anterior Insula-PCC from in vivo exposure).

Our Power Analysis (GPower 3.1) to test increased dlPFC-PCC in the MBCT group at time 2 and time 3 will be based on our pilot data (as in R61 phase) of Hedge's g = 1.44. With our proposed sample size in the optimization study (randomize N=54 in each group to conservatively obtain at least N=41 at time 2 and at least N=30 "completers" at time 3) we are sufficiently powered to detect increased dlPFC-PCC at time 2 and at time 3 (beta > 0.95). We do not yet have pilot data for an effect of previous MBCT to lead to greater decrease in Anterior Insula-PCC connectivity, but our design with N=30 per group at time 3 will be powered to detect an effect size of increased Anterior Insula-PCC connectivity in MBCT+PE vs MRG+PE effect size d=0.65 at 0.80 power (critical t=1.67), and d=0.85 with 0.95 power.

7.3 Stopping Rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial."

7.4 Designation of a Monitoring Committee

The Independent Safety Monitoring Committee for this study will comprised of two expert clinicians with longstanding expertise in PTSD and anxiety disorders (Professor Tracy Simpson, PhD of University of Washington and Professor Elizabeth Hoge, MD of Georgetown University) both with extensive experience in clinical trials for mindfulness-based interventions, an expert in PTSD psychophysiology and neurobiology (Professor Tanja Jovanovic, PhD of Emory University), and an experienced and qualified statistician (Shokoufeh Khalatbari, MS, Statistician Staff Manager, Biostatistics Program

Michigan Institute for Clinical & Health Research, The University of Michigan) who has extensive experience in managing clinical trials. These expert Independent Study Monitors are not associated with this research project and all work independently of the PI, Dr. Anthony King. They are not part of the key personnel involved in this grant, and will not have co-published with the PI within the past three years. They are qualified to review the patient safety data generated by this study because of their unique expertise. The CVs of all members of the IMC will be supplied to NCCIH for approval.

7.5 Safety Review Plan

Study progress and safety will be reviewed monthly (and more frequently if needed). Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the Independent Monitor semi-annually. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitor(s) and will be forwarded to the IRB and NCCIH. The IRB and other applicable recipients will review progress of this study on an annual basis

7.6 Study Report Outline for the Independent Monitors(s) (Interim or Annual Reports)

The study team will generate Study Reports for the Independent Monitor and will provide information on the recruitment / consent to the study, performing the intake assessment, performing the fMRI scan and associated activities, attending MBCT (or comparison therapy) sessions, turning in homework sheets, and adherence to treatment. The Study Report tables will be generated only from aggregate (not by group assignment) baseline and aggregate safety data for the study population.

7.7 Submission of On-Site Monitoring/Audit and Inspection Reports

The IRB, IMC, and NCCIH Program Officials will receive copies of all study monitoring/audit or inspection reports within 14 day of PI receipt.

7.8 Table A – Reporting Schedules

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitor(s)
Status of all enrolled subjects, as of date of reporting	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitors
Data entry quality control checks on chart review	Weekly	QA Reviewer
Adherence data regarding study visits and intervention	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitors
AEs and rates (including out-of-range lab values)	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitors
	Annually	NCCIH
SAEs (unexpected and related)	Per occurrence	PI, Independent Monitor NIH / NCCIH
SAEs (expected or unrelated)	Per Occurrence	PI, Internal QA Reviewer
	Annually	Independent Monitor, NIH/NCCIH
Unanticipated Problems	Monthly	PI, Internal QA Reviewer
	Per Policy	IRB

8 DATA HANDLING AND RECORD KEEPING

The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data collected by the team and reported, and he will be assisted by the study coordinator under his delegation. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

8.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the PI and the Clinical Trials Support Unit (CTSU) at The University of Michigan. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

8.2 Database Protection

This study will use OnCore database, an enterprise Clinical Trials Management System (CTMS) that is administered by the Michigan Clinical Trials Support Unit. OnCore is a comprehensive CTMS recently implemented at the University of Michigan Medical School and Michigan CTSU. Our study-specific database will be set up with support of CTSU and maintained by the study coordinator and data manager in coordination and oversight of CTSU administration, with electronic audit trail capability with person and date-stamp, and with oversight by CTSU and study statistician. The database will be secured with password protection. The database will not contain personally identifying information (PII), participant contact information (for study and treatment follow-up, payment, etc.) will be stored in a separate database, with a single copy of a key in a password-protected file accessible only to study coordinator and PI. The statistician and data manager will receive only coded information that is entered into the database under those identification numbers, managed by CTSU. Electronic communication with outside collaborators will involve only unidentifiable information. The database incorporates an electronic audit trail to show change(s) to data after original entry including the date/time and user making the change.

8.3 Source Document Protection

All paper and electronic source document records for all enrolled subjects, i.e., case report forms, laboratory reports, subject study binders, etc.) will be coded only by participant ID code, and will be kept in separate locked cabinets at the University of Michigan and the VA Ann Arbor

8.4 Schedule and Content of Reports

Weekly reports will be made to PI and monthly to internal QA regarding monitoring of study enrollment, study conduct, and reports for interim data analysis and study progress.

The R61 Phase is a two-group single-blinded fMRI neuroimaging study comparing MBCT intervention to a well-matched active control intervention, Muscular Relaxation Group therapy of PTSD. Interim analyses will not be performed on outcome data. The primary outcomes will be engagement of the neural target (i.e. fMRI between-groups t-test at post and group x time interaction in RM-ANOVA). Additional functional outcomes will be collected at multiple time points, including PTSD and depression diagnosis and symptom severity, and self-report measures of decentering, PTSD, rumination, and other measures. These secondary measures are exploratory but will not be included in the R61 Go/No-Go Criteria.

The R33 phase will be a single-blinded RCT comparing MBCT vs a Relaxation group therapy control, each followed by PE in vivo group. The data from the independent assessor (blinded to therapy condition) will be entered into the database; the blind on subject assignment will not be broken until the completion of recruitment and study-related activities, at which point the database will also be locked for analyses.

Interim analyses will not be performed on outcome data.

When blind is broken, we will conduct Group x Time fMRI analyses, as well as formal mediation analyses (in SEM) utilizing all unblended, locked data.

9 INFORMED CONSENT

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

To complete the informed consent process at the end of study participation, study staff will inform the subject when his/her participation has come to an end and will document the discussion in the study record.

9 REPORTING CHANGES IN STUDY STATUS

During the funding of this study, any action by an IRB, the Independent Monitoring Committee, Clinical Trials Support Unit, or one of the study investigators that results in a temporary or permanent suspension of the study will be reported to the NCCIH Program Official within 3 business days of notification.

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title:
Neural Mechanisms of Mindfulness-based Cognitive Therapy (MBCT) for Posttraumatic Stress Disorder (PTSD)

Company or agency sponsoring the study:
NIH - National Center for Complementary and Integrative Health

Names, degrees, and affiliations of the principal investigator and study coordinator (if applicable):
Principal Investigator: Anthony King, PhD, Department of Psychiatry, Michigan Medicine
Study Coordinator: Elizabeth Hinckley, BA, Department of Psychiatry, Michigan Medicine

1.1 Key Study Information

You may be eligible to take part in a research study. This form contains important information that will help you decide whether to join the study. Take the time to carefully review this information. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your family, friends, or other doctors about joining this study. If you decide to join the study, you will be asked to sign this form before you can start study-related activities. Before you do, be sure you understand what the research study is about.

A research study is different from the regular medical care you receive from your doctor. Research studies hope to make discoveries and learn new information about diseases and how to treat them. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies do not always offer the possibility of treating your disease or condition. Research studies also have different kinds of risks and risk levels, depending on the type of the study. You may also need to think about other requirements for being in the study. For example, some studies require you to travel to scheduled visits at the study site in Ann Arbor or elsewhere. This may require you to arrange travel, change work schedules, find child care, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

This research is studying the effects of different kinds of group therapy as a treatment for PTSD, and as a stress-management intervention for people with trauma history living in areas heavily impacted by the COVID-pandemic, and with elevated stress related to the COVID, and/or distress or worry (who don't necessarily have to meet current full criteria for PTSD) This research will also see how brain activity in people with PTSD is affected by the two differentMind-Body group therapies. We want to learn more about how these treatments work so we can put together better treatments for people with PTSD and for people with trauma history impacted by COVID and elevated stress and/or worry . We will provide participants with either one or the other kind of therapy (50/50 chance, like a coin toss). We will collect

information (data) about levels of PTSD symptoms using questionnaires before and after the treatment. We will also collect data about brain activity using MRI scans before and after treatment.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. For this study, some of these risks may include increase in distressing thoughts; it is possible that any psychotherapy or psychological assessment may increase distressing thoughts and dreams about your past trauma. Safeguards are in place to protect against this risk – you will have weekly contact with therapists, and will also complete brief symptom self-report measures as part of each session. For participants who do the fMRI brain scans, risks from the functional MRI scanner include minor risk of discomfort because you're lying still for more than an hour. Some people may feel more anxious from being confined in the scanner. Because we are recording the therapy sessions and your voice can be heard there is a chance that someone might be able to identify you. Being in any study or interacting with a medical system involves the possibility that someone sees your information who is not supposed to. More detailed information will be provided later in this document.

This study may not offer any benefit to you now, but then again it is possible that you might feel like your PTSD symptoms are better. Your contribution to this study may help others with PTSD in the future by increasing our understanding of how the brain and body respond to different therapies. There might be other ways to treat your PTSD including many different kinds of non-drug therapies as well as some medicines that can help with anxiety and depression symptoms. There might even be other experimental treatments. More information will be provided later in this document.

We expect the total amount of time you will participate in the study over the 10-12 weeks of the study will be 8 hrs on study-related assessment and data collection and 16 hrs of therapy. Each assessment will take about 1.5-2 hours. Additionally, you attend 8 weekly therapy sessions which are about 2 hrs each. For participnats who do the brain scans, each fMRI will take about 2 hours. You will do each of these before you start therapy and again after you finish.

You can decide not to be in this study. Alternatives to joining this study to treat your PTSD include many different kinds of non-drug therapies as well as some medicines that can help with anxiety and depression symptoms. There might even be other experimental treatments. Ask your doctor about these other options, ideally before you decide to be in this study.

Even if you decide to join the study now, you are free to leave at any time if you change your mind.

More information about this study continues in Section 2 of this document.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

The purpose of this study is to see how two different kinds of Mind-body group therapies– Mindfulness-based Cognitive Therapy (MBCT) and Muscle Relaxation Therapy are helpful for people with PTSD, and for helping with stress and worry in people living in areas heavily impacted by the COVID pandemic. We are also interested in how brain activity in PTSD patients might be differently affected by these therapies (both of these therapies can help people manage stress and are helpful for people with PTSD). We want to learn more about how these treatments work so we can put together better treatments for people with PTSD.

3. WHO MAY PARTICIPATE IN THE STUDY

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

This study is open to people ages 18-72 who either have (a) certain types of PTSD, including those with interpersonal violence, sexual assault, and combat traumas, or (b) who reside in an area that is heavily impacted by the COVID pandemic, who have trauma history, and who have elevated levels of COVID-related stress and/or worry.

Because part of the study involves getting into an MRI machine you will not be able to be in that part of the study if you are claustrophobic or are very uncomfortable lying in tight enclosed spaces, or if you have metal anywhere in your body (e.g. implanted stimulators, pacemakers, embedded metal in your skin, etc.). Having metallic braces on your teeth and fillings are OK.

3.2 How many people are expected to take part in this study?

120 people

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

If you agree to be in this study you will attend 8 weekly group therapy sessions of either Mindfulness-based Cognitive Therapy (MBCT) or Muscle Relaxation Therapy (MRT). You will not get to choose which therapy you receive. Instead you will be randomly assigned to one or the other using a computerized coin flip. You have a 50-50 chance of being assigned to each group. Before you begin a therapy group you will undergo an assessment related to your trauma history and symptoms of depression, worry, and PTSD (over a web-based online "Zoom" interview session), and fill out surveys on a secure web portal. , If you participate in the brain scan part of the study, you will come in person to UM to have an fMRI brain scan performed and provide a saliva sample. You will repeat this series of tests after you finish the 8 weeks of therapy.

As a participant in this study you have certain responsibilities. These are to protect you and to make sure the information we collect from you can be included in the study. We ask that you answer questions honestly, attend all of your scheduled appointments, and report any new or changing symptoms you might experience during the study.

Assessment Interview and Surveys

You will be asked to "meet" with a mental health provider on a remote, web-based online "Zoom" videovisit. This will be a secure and encrypted channel. We will ask you to answer a number of questions about your trauma experiences and depression and PTSD symptoms. You will also fill out surveys on a secure "web portal" asking you about your symptoms and the different ways you think about and experience things. You will do these things both before you start therapy and again after you finish therapy. This part of the study will about 1.5 - 2 hours to finish each time.

fMRI (functional magnetic resonance imaging)

If you take part in the fMRI brain scanning part of the study, you will have an MRI of your head before and after therapy to so we can look at patterns of brain activity while you look at different words. This will be on a different day from your clinical interview. Before the scan begins, you will get instructions on any study tasks. At four times (on arrive, before scan, after scan, on departure times during the session, we will collect about a teaspoon of saliva to measure your bodies level of adrenalin system function. While you are in the MRI machine you will have to lie as still as possible while your body is placed in a long, narrow tube which is the MRI camera. Just your head and upper body are in the scanner. Pictures of your brain are taken by means of magnetic pulses. You will hear loud mechanical sounds that may be unpleasant, but do not cause any sensation or discomfort. Before beginning the scan, small patches will be strapped to your fingers to measure heart rate and skin resistance. A video monitor will be placed about 15 inches in front of your eyes. You will be shown positive and negative words (like "cheerful" and "unhappy") on the screen, and asked to think about how these words may or may not describe you. In another part, you will be asked to just rest, and in another to rest and pay attention to your breath and body sensations. After the scan, you will be shown some words, and asked if you remember seeing them before. This portion of the study will take about 2 hours in total.

Therapies used in the Study

You will be assigned to either the MBCT or MRT therapy. Both will be delivered via a remote, web-based online "Zoom" videovisit. This will be a secure and encrypted channel. Both treatments involve 8 weeks of group therapy including learning mind-body skills, and both do **not** include talking about your traumatic experiences in the group. Sessions are led by mental health therapists, and will meet at the University of Michigan or VA Ann Arbor. All therapy sessions will be videotaped to help us make sure that the therapist follows the therapy plan and doesn't forget anything. You will not be seen on the video, but your voice may be heard.

Mindfulness-based Cognitive Therapy (MBCT)

Each session is approximately 2 hours long. Over the 8-week Zoom group, you will learn several mindfulness meditation techniques. You will practice paying attention to your bodily sensations, thoughts, and emotions. Each session will also involve group discussion and feedback. You will be asked to practice these techniques at home, and keep a log of your mood, and stress ratings. You will receive audio files with exercises so you can practice at home between sessions.

Muscle Relaxation Therapy (MR)

Each MR session is approximately 2 hours. Over the 8-week Zoom group, you will learn how to relax your body using a step-by-step process in which you alternate between squeezing and relaxing your muscles. You will learn about your body's natural response to stress and how to use muscle relaxation during your everyday life. Each session will also involve group discussion and feedback. You will be asked to practice these techniques at home, and keep a log of your mood, and stress ratings. You will receive audio files with exercises so you can practice at home between sessions.

Photography or video/audio.

We will video-record part of our interview (about 20 min) during the PTSD assessmentThese recordings will be rated by trained raters for emotional responses, and then destroyed. We will also video-record the therapy sessions (with the camera on the therapists) to be able to make sure the therapists are delivering the therapy correctly. The recordings will be rated by trained study team members and then destroyed

Genetic Material Data Collection

This part of the study is optional, and only for the people who do the fMRI brain scanning part of the study. We would like your permission to collect and analyze your saliva for information about your genes (DNA and RNA). We will look for changes in the expression (turning on and turning off) of certain genes like those in the immune system that might be related to PTSD and how it responds to treatment. This information will add what we know about PTSD, and help us design better treatments. To do this, we will combine the information about your DNA with the other information we collect about you for the main study (for example, MRI results, to see how different DNA profiles might be linked to different brain responses,, etc.)

This procedure requires 1 extra tube of saliva (~1 teaspoons worth) that will be collected at the same time as the saliva sample for the main study. You can be in the main study (looking at MBCT and MRT) without consenting to this additional tube of saliva and test. If you say yes today, but then change your mind later, we will do our best to destroy your sample. However, it's important to know that once your saliva sample is analyzed it might not be possible to remove the test results from our research. If your results were part of a larger set of results that we shared with collaborators, we might not be able to get it back.

Because your genetic information is unique to you, there is always a chance that someone could trace it back to you. Your saliva sample and results will not have your name on them. Instead, they will be labeled with a code that only a few people will have access to (just like in the main study). There are federal laws that protect your genetic information. GINA – or the Genetic Information Non-discrimination Act – generally makes it illegal for groups like health insurance companies and plans, and most employers, to discriminate against you based on your genes. GINA does not protect you against discrimination from life insurance companies, disability insurance, and long-term care insurance. Specifically, under this law:

- Health insurance companies and group health plans may not request your genetic information that we obtain from this research

- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums
- Employers with 15 or more employees may not use your genetic information that we obtain from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment

GINA does not apply to the following groups; however, these groups have policies in place that offer similar protections against discrimination:

- Members of the US Military receiving care through Tricare
- Veterans receiving care through the Veteran's Administration (VA)
- The Indian Health Service
- Federal employees receiving care through the Federal Employees Health Benefits Plans

Finally, because this research is paid for by the NIH we might share your genetic information in a public repository for other researchers to use. We will label your genomic information with a code, instead of your name or other information that people could use to directly identify you. Even so, there is a chance that when your genomic information is combined with other information available to researchers they might be able to identify a group you belong to (like an ethnic group or a disease population). It is far less likely that these other researchers could identify you personally. NIH prohibits people from trying to identify individuals whose genomic information is in an NIH-designated repository.

Researchers will have *controlled access* to your specific genomic information. Controlled access means that researchers will need approval from NIH in order to obtain genomic information from the repository. If you allow us to put your genomic information in the repository, you can change your mind later and ask us to remove it. Keep in mind, however, that we cannot take back information that other researchers have already obtained from the repository. The genomic summary results from this study will only be made available through controlled access.

4.2 How much of my time will be needed to take part in this study?
Each of the two assessments (Zoom interview and self-report questionnaires on the web portal) will take about 1.5-2 hours, and for people who do the fMRI scans, each of the two fMRI will take about 2 hours. You will do each of these before you start therapy and again after you finish. Additionally, you will spend 8 weeks attending 2 hr therapy sessions and practicing at home.

4.3 When will my participation in the study be over?
Your time in the study will be over after you complete the second follow-up assessment, which will be two months (8 weeks) after the completion of the 8 week (two month) therapy group) so the time in the study altogether is generally about 16-18 weeks (about four and a half months) total study time.

4.4 What will happen with my information and/or biospecimens used in this study?
Your biospecimens and collected information may be shared with our sponsor, the National Center for Complimentary and Integrative Health (part of the National Institutes of Health or NIH).

With appropriate permissions, your biospecimens and collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

We also want to keep your information linked to your identity because we might want to answer different research questions later. One thing we might want to look at is long-term effects of MBCT and MRT. So we are asking your permission to keep your information for at least 2 years after this study ends. We are also asking permission to possibly contact you again at some point in the future, to see how you're doing.

You can say no to us keeping your information after the study is over and to being re-contacted. Doing so will not change your ability to be in this study or your relationship with the study team.

5. INFORMATION ABOUT STUDY RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

There are some risks associated with being in any research study. We have described the ones we know about below, and included an explanation of how we will reduce your chance of experiencing them. There might also be risks that we don't know about or don't expect. If we learn about any new risks, we will share them with you.

Remote (online "Zoom") therapy groups and remote online psychological assessment interviews: It is possible that any psychotherapy or psychological assessment may increase distressing thoughts and dreams about your past trauma. You may feel uncomfortable disclosing your distressing thoughts to other group participants. Safeguards are in place to protect against this risk – You will have weekly contact with therapists, and will also complete brief symptom self-report measures as part of each session. The therapist will review these forms each session and set up an individual meeting with you if it looks like things are getting too distressing in that moment.

Magnetic Resonance Imaging: For those people who do the fMRI brain scans, risks from the functional MRI scanner include minor risk of discomfort because you're lying still for more than an hour. Some people may feel more anxious from being confined in the scanner. Other possible but extremely unlikely adverse effects include:

- Injury due to the main magnetic field attracting ferromagnetic/metallic objects towards you.
- Temporary hearing loss due to loud noises associated with fMRI scanning.
- Potential of exacerbated psychiatric symptoms (such as increased anxiety, panic, or PTSD symptoms) when going into the fMRI scanner
- Fast imaging sequences, such as those employed in this study, have the potential to induce peripheral nerve stimulation (PNS). PNS can be described as light touching sensation on the skin surface and may cause mild discomfort, but is not harmful to the subject. The MRI machine is operated within FDA guidelines so the potential for inducing PNS is very low.
- Transdermal medication patches that are placed on the skin to deliver a time release dose of medication through the skin and into the bloodstream, like nicotine patches like those that

deliver nicotine, testosterone and nitroglycerin, can cause burns if worn during an MRI procedure. That's because some transdermal patches have an aluminized backing.

To reduce any potential risks, the following will be done: Anyone allowed in the room will be screened for metallic objects prior to entering the scan room to minimize the risk of the main magnetic field attracting ferromagnetic/metallic objects towards the magnet. We will also screen for transdermal medication patches. You will be required to wear foam earplugs or other hearing protection, as is routine for clinical patients, to prevent risk of hearing damage due to the inherently loud noise of MR scanning. The risk of discomfort will be minimized by custom pads and pillows to make you as comfortable as possible.

You will be able to talk with the operator or researcher through an intercom at all times during the scan and will also be able to trigger an audible alarm (using a squeeze ball held in left hand) at any time if you are feeling uncomfortable or experiencing feelings of anxiety or panic for immediate attention or to get out of the MRI machine. If, at any point during your time at the MRI facility you experience discomfort, you should inform the investigator and the study can be stopped at any point. If you experience anxiety, panic, or worsening of PTSD symptoms you will be provided counseling by the PI or other study team members who are licensed psychologists or psychiatrists at the MRI facility or another place later that day. If necessary we will refer you for additional care that day or options for additional or alternate care, and we will follow up with you over the next few days to see how you are doing and if you need further assistance or referral.

There is also a chance that the MRI will reveal abnormalities in the brain, e. g. a tumor, previously unknown to you. While the research team is not formally trained to diagnose brain abnormalities from MRI images, if an abnormality is detected on an MRI image, we will notify you and help advise you about what to do next.

Video & Audio recording: Audio-video recordings of the interview and therapy sessions will stored on a secure, encrypted, HIPPA-compliant UM computer server and/or on a hard drive kept in a locked cabinet in UM research office space. The recordings will be reviewed and rated by trained study team staff, and they will be permanently destroyed after they are rated.

Privacy and Confidentiality: Being in any study or interacting with a medical system involves the possibility that someone sees your information who is not supposed to. We talk about these kinds of risks in Section 9 of this form.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?

Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You may not receive any personal benefits from being in this study, but then again it is possible that you might feel like your PTSD symptoms are better. Your contribution to this study will help future PTSD patients by increasing our understanding of how the brain and body respond to different therapies.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. ALTERNATIVES TO PARTICIPATING IN THE STUDY

6.1 If I decide not to take part in this study, what other options do I have?
There can be other ways to treat your PTSD and/or stress and worry including many different kinds of non-drug therapies as well as some medicines that can help with anxiety and depression symptoms. There might even be other experimental treatments. Ask your doctor about these other options, ideally before you decide to be in this study.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?
You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 “Contact Information”.

7.2 Could there be any harm to me if I decide to leave the study before it is finished?
No

7.3 Could the researchers take me out of the study even if I want to continue to participate?
Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?
There are no costs or billing for this study. By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?
You will be paid (in the form of a gift card given to you in person or a check mailed to your house) for finishing each segment of the study up to a total of $345:

- $25 for each clinical assessment (Zoom interviews & surveys)
- $120 reimbursement for use of two months personal internet / data services for Zoom, or if I do not have current secure internet and Zoom capable device, I will be provided a Zoom-capable smart phone and sufficient months of unlimited data plan to complete the study

Participants who do the brain scan part of the study will be paid $75 for each fMRI scan

8.3 Who could profit or financially benefit from the study results?
No one associated with this study will profit or benefit financially from the study results.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how the confidentiality of your research records will be protected in this study, and any sub-studies described in this document.

9.1 How will the researchers protect my information?

- Only authorized people can access your information and saliva sample.
- We keep your information, including things that identify you like your name or phone number, password-protected and restricted-access databases that are protected by Michigan Medicine computer systems.
- Paper records that have your name on them, like this document, are kept separate from your other research records. We keep these records in locked cabinets in locked offices.
- Recordings of therapy sessions are stored in password-protected restricted-access database.
- Your saliva samples are not labled with your name. Instead we use a study code on these things so that it's harder for someone to know that it's yours.
- The link between your name and the study code is kept confidential and only available to authorized study team members. Your name or other things that identify you will not be included in any reports or publications.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the SPONSOR which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of child abuse and neglect, or harm to self or others.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

Because this study is sponsored by the NIH your information and saliva samples are also protected by a Certificate of Confidentiality. This means that we cannot be forced to disclose or use any of your private identifiable information (e.g. documents, saliva sample, other study information) that might identify you in any federal, state, or local civil, criminal, administrative, legislative, other or proceeding (e.g. court subpoena) unless you give us permission.

Information, documents, or saliva samples protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except when:

- There is a federal, state, or local law that requires us to, like in cases of child abuse or communicable diseases
- You have consented to the disclosure, including for your medical treatment

It is used for other scientific research as allowed by federal regulations protecting research subjects

Clinicaltrials.gov

A description of this clinical trial will be available on http://www.clinicaltrials.gov/, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

9.2 What protected health information (PHI) about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study.

Medical information and billing records are protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). This type of information is called protected health information (PHI). PHI about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Mental health care records (except psychotherapy notes not kept with your medical records)
- Alcohol/substance abuse treatment records
- HIV/AIDS status
- Sexually transmitted disease and/or other communicable disease status
- Genetic counseling/genetic testing records
- Health plan/health insurance records
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information
- Demographic information
- Personal identifiers
- Other information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA) and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, Social Security number, payment amount, and related information for tax reporting purposes.

- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission to use my PHI?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities. (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission to use my PHI expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Anthony King, PhD
Mailing Address: 2747 Rachel Upjohn Building / 4250 Plymouth Road, Ann Arbor, MI 48109
Telephone: 734-936-4955

Study Coordinator: Elizabeth Hinckley, BA
Mailing Address: Rachel Upjohn Building / 4250 Plymouth Road, Ann Arbor, MI 48109
Telephone: 734-764-9527

You may also express a question or concern about a study by contacting the Institutional Review Board listed below:

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies, include the appropriate calling codes.)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.
When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*

12. SIGNATURES

Sig-A

Consent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with [NAME OF STUDY TEAM MEMBER OBTAINING CONSENT] _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Sig-B

Consent to video & audio recording for purposes of this research

This study involves video and/or audio recording and/or photography. If you do not agree to be recorded, you cannot take part in the study.

_____ Yes, I agree to be video/audio recorded/photographed.

_____ No, I do not agree to be video/audio recorded/photographed.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Sig-D

Consent to Collect for Unspecified Future Research

This project involves the option to allow the study team to keep your identifiable saliva for use in future research. I understand that it is my choice whether or not to allow future use of my specimens. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to let the study team keep my saliva for future research.

_____ No, I do not agree to let the study team keep my saliva for future research.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Sig-x

Consent to be contacted again for later research

We might want to contact you in the future. You can say "yes, re-contact me" today, and change your mind later. If you change your mind, please call us so we can take you off the re-contact list.

There are different reasons why we might want to contact you again. For example, we might want to see if there are any long-term effects of MBCT or MRT. Saying no does not impact your eligibility for this study.

_____ Yes, I agree to being re-contacted.

_____ No, I do not agree to being re-contacted.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Sig-C

Consent to Participating in an Optional Procedure – Genetic Material Data Collection

This project involves an optional saliva test for genetic analysis. I understand that it is my choice whether or not to take part in this extra test. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to take part in the optional sub-study.

_____ No, I do not agree to take part in the optional sub-study.

Print Legal Name: _____

Signature: _____

Sig-G

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Printed Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____