University of Colorado Boulder

TITLE: Neural effects of wellness classes in women with vulnerability to depression ("The Women's Wellness Study")

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I. OBJECTIVES

This project aims to characterize the psychological, physiological, and neural mechanisms underlying symptoms of depression as well as the neural and psychological effects of an eight-week mindfulness based cognitive therapy (MBCT) intervention in preventing depression among women with past history of major depression. We also aim to develop informative brain biomarkers able to accurately predict future remission/relapse 6 months following the interventions.

II. BACKGROUND AND SIGNIFICANCE

Major depression is estimated to be the fourth leading contributor to disease and suffering world-wide (Murray and Lopes, 1998), showing prevalence rates between 2.9% and 12.6% (Kessler et al. 1994; JAMA, 2003). It is also characterized by a markedly chronic nature (Judd, 1997); patients experience on average 4.3 major depressive episodes (Perris, 1992), with each additional episode significantly increasing the future probability of relapse (APA, 2000; Bhagwagar and Cowen, 2008). Therefore, addressing MDD prophylaxis and understanding the pathogenic mechanisms involved in depressive relapse are essential to guide tailored selection of preventive interventions on an informed basis.

Compelling evidence suggests that Mindfulness Based Cognitive Therapy (MBCT) has beneficial effects in preventing depressive relapses when compared to treatment as usual, placebo or psycho-education interventions[8-15], and similar effects when compared with antidepressant pharmacotherapy[9]. Initial evidence points out that reductions in residual symptomatology after MBCT seem to be mediated by a reduction in worry and rumination, together with increases in mindfulness skills and self-compassion[13-15]. One recent study[15] showed that MBCT is able to disrupt the relationship between cognitive reactivity – ruminative thought- after sad mood induction and symptoms of depression in remitted patients. With the exception of such scarce literature on the subjective effects of MBCT, there are no previous studies addressing the behavioral and, more specifically, the neural underpinnings of the beneficial effects of MBCT on relapse prevention in remitted patients with previous recurrent history of depression.

Given this context, efforts to prevent depression hold obvious appeal. Mindfulness-based cognitive therapy (MBCT) represents one of the most important recent developments in the effort to prevent recurrent depression (Segal, Williams, & Teasdale, 2001). Explicitly designed to modify core underlying vulnerability factors among recovered individuals with histories of depression, MBCT may have high applicability to the prevention of MDD.

MBCT is based on Mindfulness-Based Stress Reduction (MBSR), combining principles of cognitive therapy (CT) with those of mindfulness meditation to prevent depression relapse. Both MBSR[1] and MBCT use contemplative practices, including sitting meditation, body scan and walking meditation, as core methods to teach awareness of negative thoughts and emotions with the aim of disengaging from pervasive patterns of ruminative self-centered mentation. Compelling evidence suggests that MBCT has significantly greater beneficial effects in preventing depressive relapse than placebo or psychoeducation interventions[3-10] and comparable effects as maintenance antidepressant pharmacotherapy[11].

There is an emerging body of literature[12,13] on the specific mechanisms of action of MBSR suggesting (i) increased non-judgmental awareness of the contents of consciousness and their transitory nature,[2,14] (ii) reduced ruminative thinking[15-17] and emotional reactivity[18-21] with augmented self-compassion[2,19,27], and (iii) increased capacities in the domains of attention, working-memory and cognitive flexibility[22-27]. In contrast to this compelling evidence, there is a scarcity of empirical support as to the psychological and neural mechanisms underlying the beneficial effects of MBCT in preventing depression relapse. Only recent preliminary data, relying predominantly on self-report questionnaire methods, suggest that reductions in residual symptomatology after MBCT is mediated by a reduction in worry and rumination, with concurrent increases in self perceived mindfulness, sleep improvements and self-compassion[28-32].

Recent imaging studies of MBSR[33-37] suggest that mindfulness meditation promotes a shift from more "narrative" to "experiential" forms of self-related awareness. Narrative self-focus refers to a concept of self that is extended in time, including past memories and intentions for the future, together with abstract self representations in relation to socio-emotional values. In contrast, the "experiential self-focus" refers to a more immediate self experience and is associated with greater awareness of external stimuli and internal somatic-visceral bodily states. MBSR has been shown to increase brain activity in regions relevant for conferring "experiential" self-focus (insula-opercula, dorsal anterior cingulate/supplementary motor area), while decreasing responses in rostral-medial, lateral frontal and hippocampal regions that support the "narrative" mode of self-focus. Such changes in brain activity are associated with increased well-being[35-37,12,13].

The extension of these findings to the practice of MBCT is particularly important given the central role of mindfulness meditation and the specific vulnerabilities associated with recurrent depression. Research suggests that among individuals with histories of depression, episodes of stress increase dysphoria and activate analytical ruminative thinking about past events with strong "narrative" self-focus, which is congruent with their easy access to negative self-relevant material (e.g. self-criticism, dissatisfaction and blameworthiness)[38,39]. Rumination then intensifies the dysphoric state and increases relapse risk[38-39]. These ideas and some of the observations grounded the development of MBCT as a prophylactic intervention for recurrent depression[1,43].

Brain imaging studies have provided parallel information on the neural underpinnings of increased vulnerability for depression[44-53]. These studies suggest that structural, functional and biochemical alteration in specific elements within two major functionally-connected brain networks, the "default

mode" (DMN) and the "insular-paralimbic" (PLN) networks, are involved in the generation and maintenance of depressive episodes. Importantly, activity and connectivity balances within and between these two brain networks have shown to be responsible for either greater "narrative" or "experiential" self-focus[33-37]. Interestingly, neural activities in these two brain systems are strongly negatively correlated[54]. It has repeatedly been shown that ruminative self-related tendencies, depressive symptom severity and augmented fear are associated with enhanced activity within DMN components[33-35,55-58]. On the other hand, augmented perception of visceral autonomic and somatic information, such as attention focused on heart-beating or breathing, enhance activity within the PLN[59-62].

In summary, a wealth of evidence suggests that (i) Women that have experienced at least one past episode of depression are at high risk of relapse and there is need for new psychosocial prophylactic interventions guided to prevent depression relapse in such populations, (ii) MBCT interventions effectively reduce risk for depressive relapse in chronic depressive patients, (iii) enhanced narrative (vs experiential) self-focus and negative rumination are associated with high risk for depression relapse, (iv) neural systems conferring vulnerability for depression highly overlap with those responsible for different forms of self-referential focus ("narrative" and "experiential") and (iv) MBSR promotes the transition from more "narrative" to more "experiential" modes of self-focus, which is associated with enhanced subjective well-being and reduced stress-related responses. Despite this growing body of research, the specific psychological and neurobiological mechanisms underlying the positive effects of MBCT as a prophylactic intervention for depression remains unknown.

III. RESEARCH STUDY DESIGN AND PROCEDURES

Overall, this study aims to characterize the neural and psychological effects of an eight-week mindfulness based cognitive therapy (MBCT) intervention (online group class) in preventing depressive relapse in women with past history of major depression when exposed to different forms of self-relevant and context-specific emotional challenge. We also aim to establish psychological and neural mechanisms contributing to depressive symptoms prior to intervention and develop informative brain biomarkers able to accurately predict future remission/relapse 6 months following the interventions. A key objective of the study is to assess baseline markers of depressive symptoms and possible change resulting from the MBCT intervention from interdisciplinary perspectives, including the **psychological perspective** (i.e. measured with computer-based tasks, self-report ratings, questionnaires, etc.), the **physiological perspective** (i.e. heart rate, skin conductance, and respiratory response upon viewing emotional and non-emotional material), and the **neural perspective** (neural activity measured with functional MRI). We aim to uncover how differences in emotional well-being across individuals manifest both in the lab and in daily life.

Overview of Design and Procedures:

We aim to enroll two groups of participants in this study. Extensive behavioral and clinical measurements will be collected at baseline for both groups.

Group 1: Group 1 (healthy control participants) will comprise women with no prior history of depression or other mental health disorders. Participants in group 1 will be asked to:

- Undergo a clinical interview and a series of behavioral tasks (session 1)
- Answer several self-report questionnaires administered online (at home session)

- Answer questions about their daily mood and thoughts over a period of approximately 10 days (at home)
- Return to the laboratory for an MRI session and additional behavioral tasks (session 2)
- Return to the laboratory for a second MRI/behavioral session after 8 weeks (an equivalent duration as the intervention administered to Group 2).

Group 2: Group 2 will comprise women with a prior history of depression who lack other exclusion criteria (see below). Participants in group 2 will be asked to undergo the same procedures requested of group 1 participants, as well as to complete an 8-week intervention and 6-month follow-up assessments. Thus, group 2 participants will be asked to:

- Undergo a clinical interview and a series of behavioral tasks (session 1)
- Answer several self-report questionnaires administered online (at home session)
- Answer questions about daily mood and thought content over a period of approximately 10 days (at home). Right after this assessment, we may include a baseline period of up to 4 weeks, in which we would ask the patient to complete a subset of the questionnaires including the PHQ-9 to assess the stability of the symptoms (to have a measure of changes in symptomatology due to natural history/regression to the mean).
- Return to the laboratory for an MRI session and additional behavioral tasks (session 2)
- Complete an 8-week at home MBCT intervention (see below) and answer weekly questionnaires about mood and thoughts over the course of the intervention
- Return to the laboratory for a post-intervention MRI session and the same behavioral tasks as completed prior to the intervention
- Complete the same set of self-report questionnaires as completed prior to the intervention (at home session)
- Answer questions about daily mood and thought content over a period of approximately 10 days (at home)
- Undergo a clinical assessment approximately 6 months post-intervention and complete self-report questionnaires

The 8-week online MBCT intervention

Participants in group 2 will be asked to complete an 8-week online MBCT intervention following session 2. MBCT will be delivered in 8 'online group sessions', featuring an initial orientation and including guided mindfulness and yoga practices, cognitive-behavioral strategies, and psychoeducation procedures, consistent with standard MBCT. The following table outlines the topic and targets of each session (Table 1).

Table 1. Description of MBCT sequence of session topics and targets.

#	Topic	Targets
1	Orientation to MBCT	Rationale for daily practice not tied to symptom presence, facing difficulties, patience and persistence; enhancement of motivation.
2	Automatic pilot	Recognizing cognitive, behavioral, and affective automatic patterns and how such automaticity can be associated with increased risk of relapse/recurrence during periods of sad mood; committing to mindfulness practice as a means of stepping out of automatic pilot

3	Dealing with barriers	Practicing moving attention to specific foci to learn that attention can be intentional as opposed to automatic; identifying barriers to mindfulness practice that arise, with specific focus on automatic cognitive patterns
4	Mindfulness of breathing	Increasing awareness of how often the mind is busy/scattered; introducing key formal practices including mindfulness of breathing, walking, and yoga
5	Staying present	Increasing awareness of the ways avoidance or clinging to particular experiences can be associated with depression; practicing a new mode of responding that stays present and attentive in the face of difficulty; identifying symptoms and cognitions characteristic of depression as early warning signs
6	Allowing and Letting be	Increasing use of mindful attention at the first step in responding effectively to difficulties, including difficult internal experience such as sadness; decreasing judgmental thoughts and avoidant responses to difficulties
7	Thoughts are not facts	Decreasing affective reactivity to thoughts previously associated with depression; learning to "de-center" from difficult thoughts, realizing that thoughts are merely thoughts; recognizing patterns of recurring thoughts
8	How can I best take care of myself?	Identifying unique warning signs of relapse ("relapse signature"); identifying activities that improve or deteriorate mood; developing action plans to implement during periods of high risk; using mindfulness practice explicitly to guide action plan steps

As in previous studies, before interviewing the potential participants, we will ask them to complete an online screening form (see Attachment_6, Attachment_7 and Attachment_8 in Table 3) using CU's secure survey system provider, i.e., RedCap (for a detailed description see Recruitment Methods). Before the formal intervention begins, we will address subjects' possible reluctance to devote time to self-care during a period of symptom quiescence. We will present information about MBCT in the orientation session within a broader motivational context aimed at enhancing subjects' intrinsic motivation to practice mindfulness (or homework exercises) by exploring and resolving possible ambivalence.

As part of the intervention, participants will be encouraged to engage in the intervention modules and complete supplementary "homework" 6 days per week, measured using a daily practice record online.

Weekly phone coaching based on the modified telecoach manual developed by Mohr and colleagues (Duffecy et al. 2010) will be provided by clinical graduate students, under the supervision of Dr. Dimidjian, and Dr. Segal. Phone coaching will include two initial engagement sessions that will last ~30 minutes, and follow up calls are anciticapted to last 5-10 minutes (after sessions 1 and 2). The coach and participant collaboratively decide whether to continue phone calls or transition to weekly email support after the second session. Participants also are reminded that they can always resume phone calls if they prefer them to the email support.

In the following sections we will provide a detailed explanation of the (a) clinical interviews and cognitive functioning battery, (b) psychological scales and questionnaires, (c) specific cognitive-emotional experimental tasks, and (d) naturalistic thought sampling that will be measured before and after the interventions. We also provide a summary of the timeline of the study.

- (A) CLINICAL INTERVIEWS AND COGNITIVE FUNCTIONING BATTERY

All subjects will have an introductory session where they will receive all relevant information about the study. The same day they will be asked to carefully read, ask about and sign the written informed consent. Demographic and clinical information will be registered for every subject. The ***Structured Clinical Interview for the DSM-V-RV, Research Version*** will be administered. The SCID-V-RV (First, Spitzer, Gibbon, &Williams, 1996; see Attachment_9 in Table 3) is a semi-structured psychiatric interview designed to yield judgments with respect to all five axes in the DSM-V. The SCID-V-RV is widely used for diagnostic purposes in clinical and research settings, and will be given by research staff who are trained in implementing and coding the interview. The SCID-V-RV is modular in format, with each DSM-V disorder investigated separately. The research interviewer begins each module with screening questions, and depending upon the participant's report, may continue to query for more information regarding symptoms or may skip to the next module. Furthermore, the SCID allows for assessment of both current and history of clinical disorders, and the Global Assessment of Functioning Scale (GAF; Luborsky, 1962) to assesses overall psychological, social, and occupational functioning on a scale from 1 (lowest level of functioning) to 100 (highest level of functioning). We will audio-record the clinical interview for a subset of the patients only for research purposes (which will not include the participant's name, address, or date of birth) in order to determine inter-judgement reliability assessments. As we discuss in detail below, all of the participants' information will be kept strictly confidential and will be only used for research purposes. We will store the clinical audio-recording files (identified only by participants' study ID) in an external hard drive designated for the study, located in a locked file cabinet within a locked room within Sona Dimidjian's CREST lab. Audio data will be retained indefinitely on encrypted, password protected, and firewalled servers in the Department of Psychology and Neuroscience.

At post-intervention and at 6 months follow-up post-intervention, we will use the Longitudinal Interval Follow-up Evaluation (LIFE, please see Attachment_10 in Table 3) to ascertain subsequent diagnostic status, again according to DSM-V diagnostic criteria. The LIFE provides a retrospective assessment of relapse and recurrence based on a semi-structured interview.

- (B) PSYCHOLOGICAL MEASURES (SCALES AND QUESTIONNAIRES)

For both groups, several psychological constructs will be measured pre-intervention, post-intervention and, for a subset of questionnaires, 6 months after the end of the intervention. Note that for Group 1, this will occur 8 weeks after the session 2, and 6 months after that. We summarize the main constructs of interest below.

1. Depression and anxiety.

We will use the 21-item Beck Depression Inventory II (BDI; Beck, Steer, & Brown, 1996; please see Attachment_11 in Table 3), which is the most widely used measure of depression in intervention studies, and the Patient Health Questionnaire (PHQ-9, Kroenke et al. 2001, please see Attachment_12 in Table 3). We have added the section entitled 'Management of Potential Clinical Deterioration and Suicidal Ideation', please see page 14, in order to explain how these measures will be used for ongoing safety monitoring.

To assess generalized anxiety symptoms we will administer the GAD-7 (Spitzer et al. 2006, Attachment_13 in Table 3).

2. Rumination and cognitive reactivity.

The 22-item Ruminative Response Scale (RRS; Nolen-Hoeksema 1987, 1999; please see Attachment_14 in Table 3) will be used to assess the degree to which people tend to ruminate when they are feeling down, sad, or depressed. The scale consists of a list of possible things that people could do, in general, when they are feeling down or sad. Example items include: "Think about how alone you feel" and "Go someplace alone to think about your feelings." Items are answered on a 4-point scale (1=almost never and 4=almost always).

To measure excessive and uncontrollable worry, we will administer the 16-item Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990; please see Attachment_15 in Table 3). This questionnaire measures people's tendency to worry about things in general and does not ask about whether people worry about any specific types of situation or events, and therefore allows a measurement of worry that is distinctively different from the constructs of either depression or anxiety. Example items include: "Many situations make me worry," "I never worry about anything," and "Once I start worrying, I can't stop." Items are answered on a 5-point scale (1 = Not at all typical and 5 = Very typical). Lastly, we will include the Leiden Index of Depression Sensitivity (LEIDS-R, Van Der Does, 2002; Attachment_16 in Table 3).

We are also including a validated measure of self-concept (Twenty Statements Test, Kuhn and McPartland, 1954; Attachment_53 in Table 3) and of Cognitive Behavioral Avoidance (Ottenbreit and Dobson, 2002; Attachment_54 in Table 3).

3. Perceived Stress.

The 14-item *Perceived Stress Scale* (PSS) is a measure of the degree to which situations in one's life are appraised as stressful (Cohen, S., Kamarck, T. & Mermelstein, R., 1983; please see Attachment_17 in Table 3). The PSS has been validated in both clinical and community samples, and shows high reliability with alpha = .84 to .86. The scale was additionally found to correlate positively with number of life events, impact of life events, and to be a better predictor of health and health-related outcomes than simple life-event scales. Items are rated on a five-point scale indicating how often they have experienced specific feelings and thoughts in the past month.

4. Positive and Negative Affect and Empathy.

The 20-item Positive and Negative Affect Scale (PANAS; Watson & Clark, 1994; please see documents Attachment_18 and Attachment_19 in Table 3) is the gold standard assessment of affect used in clinical research. Both subscales of positive and negative affect are found to have high internal consistency (Cronbach's alpha of .83 to .91) for clinical and community samples. Separate questionnaires encourage participants to rate each item based on the extent to which they feel that way *currently* (in the moment), or *in general*. Example items include: "interested" and "distressed." Items are rated on a five-point scale.

To specifically assess positive affect and beliefs about positive emotions and affective states, which are susceptible to change following the intervention, we will include the following measures: Affect Valuation Index (Tsai et al. 2006, Attachment_20 in Table 3), Emotion Beliefs Scale (Rimes et al. 2010, Attachment_21 in Table 3), Happiness Beliefs Scale (Gruber et al. 2014, Attachment_22 in Table 3), the Emotion Regulation Valuation Index (Attachment_23 in Table 3). Lastly, we will include the *Hypomanic Personality Scale (HPS-24, Attachment_24* in Table 3*).* We are also including the Positive Empathy Scale

(Morelli, 2012; Attachment_56 in Table 3) and the Interpersonal Reactivity Scale including Empathic Concern subscale (Davis, 1980; Attachment_57 in Table 3).

5. Mindfulness.

The 39-item *Five-factor Mindfulness Scale* (FFMQ; Baer, Smith, Hopkins, Krietemeyer & Toney, 2006; please see document Attachment_25 in Table 3) assesses five domains of mindfulness, including acting with awareness, non-reactivity, observing, describing, and non-judging. This measure is widely used to capture individual differences in mindfulness strategies. Items are rated on a five-point scale.

The 20-item *Experiences Questionnaire* (EQ) has a 2-factor structure that evaluates rumination and decentering (Fresco, Moore, Dulmen, Segal, Ma, Teasdale, & Williams, 2007; please see document Attachment_26 in Table 3). The decentering scale of the EQ shows significant negative relationships with concurrent levels of depression and anxiety symptoms and theoretically meaningful associations with constructs including depressive rumination, experiential avoidance, and emotion regulation (Fresco et al., 2007, p. 244). Items are rated on a 5-point scale ranging from 1 "never" to 5 "all the time."

We will include the Imaginal Process Inventory, specifically the mind wandering and thought fluency subscales (IPI, Singer et al., 1963;Mason et al., 2007; please see Attachment_27 and Attachment_28 in Table 3).

6. Psychological and physical well-being.

The 54-item RYFF (Ryff, 1989; please see document Attachment_29 in Table 3) measures 6 dimensions of psychological well-being: autonomy, environmental mastery, personal growth, positive relations with others, purpose in life, and self-acceptance. These dimension scales (9-items each) have high internal consistency ranging from 0.83 to 0.91. The items are rated on a scale of 1 (strongly disagree) to 6 (strongly agree). We will also include the SF-12 (Attachment_30 in Table 3; Ware, 2006) which is a brief self-report measure of mental and physical functioning and overall health-related-quality of life and a few more demographical and health related questions (Attachment_31 in Table 3). Sleep quality (Attachment_32 in Table 3; Buysse et al. 1989), and physical activity (Attachment_33 in Table 3; Hagströmer et al. 2006) will also be assessed.

7. Self-compassion.

Self-compassion involves "being open to and moved by one's own suffering, experiencing feelings of caring and kindness toward oneself, taking an understanding, nonjudgmental attitude toward one's inadequacies and failures, and recognizing that one's experience is part of the common human experience". The Self-Compassion Scale (SCS: Neff, 2003; please see Attachment_36 in Table 3) measures how individuals typically act and react towards themselves in difficult times. It particularly addresses the ability to treat oneself with kindness when things go badly. It specifically measures *self-kindness,* self-Judgment, common humanity, isolation and mindfulness.

8. Social Support.

We will assess social support with the Social Support Questionnaire, short form (please see Attachment_37), which yields measurements of the size of the social support network and the satisfaction with available supports. It has excellent construct and discriminant validity as well as strong internal consistency and test-retest reliability.

9. Bodily *Pain and Fatigue.*
Considering the relationship between pain complaints and depression (Launtenbacher et al. 1993; 1994; Gieseche et al, 2005), we will assess clinical pain complaints pre and post intervention using the Brief Pain Inventory-short form (please see Attachment_38 in Table 3). We may also use the Pain Catastrophizing Scale (PCS, Sullivan et al. 1995-2009, Attachment_39 in Table 3). In order to measure fatigue in our sample, we are including the Multidimensional Fatigue Inventory (Smets et al. 1995; Attachment_55 in Table 3).

10. Expectations about treatment outcome and client satisfaction.
To measure the effects of expectations on intervention outcomes, will administer the Credibility/Expectancy Questionnaire (CEQ, Devilly, G. J., & Borkovec, T. D. 2000, Attachment_40 in Table 3) and a modified version of the BDI and PHQ-9 questionnaires (see Attachment_41 and Attachment_42 in Table 3) in which the questions refer to participants' expectation of improvement in each clinical domain (e.g., sadness) after receiving the intervention. To measure client satisfaction, we will administer the Client Satisfaction Questionnaire (CSQ, Attkisson & Greenfield, 2009; Attachment_43 in Table 3).

The following Table 3 provides a summary of all data collection instruments/measures/attachments to be completed in this study, including additional validated questionnaires not summarized above.

Table 3. Summary of all attachments (i.e. instruments, scales, letters of support, etc.) to be completed in the WWS study.

#	Topic	**content**
0	Protocol	Protocol
1	Attachment 1	Consent Form Group 1
2	Attachment 2	Consent Form Group 2
3	Attachment 3	Empty attachment. Removed.
4	Attachment 4	Flyer 1 for control women
5	Attachment 5	Flyer 2 for women at risk
6	Attachment 6	Pre-screening online consent form
7	Attachment 7	Screening questions, old OnlForm_mod document
8	Attachment 8	Screening PDSQ, i.e., Psychiatric Diagnostic Screening Questionnaire
9	Attachment 9	SCID. Structured Clinical Interview DSM-V-RV, Research Version
10	Attachment 10	LIFE-Rift. Longitudinal Interval Follow-up Evaluation
11	Attachment 11	BDI-II. Beck Depression Inventory II
12	Attachment 12	PHQ-9. Patient Health Questionnaire
13	Attachment 13	GAD-7. Generalized Anxiety Disorder symptoms
14	Attachment 14	RRS. Ruminative Response Scale
15	Attachment 15	PSWQ. Penn State Worry Questionnaire
16	Attachment 16	LEIDS-R. Leiden Index of Depression Sensitivity
17	Attachment 17	PSS. *Perceived Stress Scale*
18	Attachment 18	PANAS. Positive and Negative Affect Scale, last week.
19	Attachment 19	PANAS-NOW. Positive and Negative Affect Scale, right now.
20	Attachment 20	AVI. Affect Valuation Index
21	Attachment 21	EBS. Emotion Beliefs Scale
22	Attachment 22	HBS. Happiness Beliefs Scale
23	Attachment 23	ERVI. Emotion Regulation Valuation Index
24	Attachment 24	HPS-20. *Hypomanic Personality Scale*

25	Attachment 25	FFMQ. *Five-factor Mindfulness Scale*
26	Attachment 26	EQ. *Experiences Questionnaire*
27	Attachment 27	IPI-MW. Imaginal Process Inventory- Mind Wandering
28	Attachment 28	IPI-TF. Imaginal Process Inventory- Thought Frequency
29	Attachment 29	Ryff Scales. Psychological well-being scales
30	Attachment 30	SF-12. Mental and physical functioning
31	Attachment 31	Demog_Health_Medit_ShortForm Questionnaire
32	Attachment 32	PSQI. Pittsburgh Sleep Quality Index
33	Attachment 33	IPAQ. International Physical Activity Questionnaire
34	Attachment 34	Empty attachment. Removed.
35	Attachment 35	Empty attachment. Removed.
36	Attachment 36	SCS. Self-Compassion Scale
37	Attachment 37	SSQ. Social Support Questionnaire
38	Attachment 38	BPI. Brief Pain Inventory-short form
39	Attachment 39	PCS. Pain Catastrophizing Scale
40	Attachment 40	CEQ. Credibility/Expectancy Questionnaire
41	Attachment 41	BDI-II Expected Improvement
42	Attachment 42	PHQ-9 Expected Improvement
43	Attachment 43	CSQ. Client Satisfaction Questionnaire
44	Attachment 44	Safety.
45	Attachment 45	Autobiographical Memory Interview
46	Attachment 46	Phone Screening Patients WWS
47	Attachment 47	Phone Screening Controls WWS
48	Attachment 48	Letter Collab. Dr. Zindel Segal
49	Attachment 49	Letter Collab. Dr. Norman Farb
50	Attachment 50	Mini-Mental State Exam, MMSE.
51	Attachment 51	Empty attachment. Removed.
52	Attachment 52	List of referral options in case excluded during screening for diagnosis
53	Attachment 53	Twenty Statements Test (TST)
54	Attachment 54	Cognitive Behavioral Avoidance Scale (CBAS)
55	Attachment 55	Multidimensional Fatigue Inventory
56	Attachment 56	Positive Empathy Scale
57	Attachment 57	IRI Interpersonal Reactivity Index (a measure of negative empathy)
58	Attachment 58	Naturalistic Thought Sampling Questionnaire
59	Attachment 59	Document to track Medication Use
60	Attachment 60	Flyer 1b generic flyer for control women and women at risk
61	Attachment 61	fMRI Release Form
62	Attachment 62	Experience Sampling Weekly questionnaire ES_Weekly
63	Attachment 63	Mind Wandering Questionnaire
64	Attachment 64	NAART35_10-12-07 questionnaire
65	Attachment 65	NAART35_WORD.LIST Word list for previous questionnaire
66	Attachment 66	Psychotherapy form. To assess concurrent psychotherapies
67	Attachment 67	Spontaneous deliberate mind wandering questionnaire, to assess everyday mind wandering

Management of Potential Clinical Deterioration and Suicidal Ideation

Participants will be asked to complete the PHQ9 at evaluation contact and weekly throughout the duration of the intervention phase of study for Group 2. Each time a participant completes the PHQ9 on Qualtrics, an email trigger containing the de-identified response data will be sent to the study coordinator. This allows for ongoing monitoring of depression symptom severity. If participants report any suicidal ideation on online questionnaires, we will not provide additional assessment to determine level of risk, but will provide all subjects who report any suicidality with national and local mental health referral information. Thus, if a participant endorses suicidal ideation, branching logic in the questionnaire will display the statement:

> "Thank you for being willing to take a few minutes to answer questions about how you are doing. The study staff may not immediately review your responses to these questions and will not be responding to thoughts about death or hurting yourself. Thoughts about death or hurting yourself are serious, but not uncommon. Because you indicated that you may be having these thoughts, we want to be sure you know how to access support from the National Suicide Prevention Lifeline (available 24/7) at 1-800-273-8255. There are also a number of local and regional resources including:
> - The Colorado Crisis Services at 844-493-8255
> - The Colorado Mental Wellness Network at 720-842-9222
> - The Mental Health Center of Denver at 303-504-6500
>
> If you think you are in danger of hurting yourself, call 911 or go to the nearest emergency room."

Decisions about continuation in the study protocols will be made on a case-by-case basis by Dr. Dimidjian. Generally, we intend to continue all participants in the study unless doing so would present complication for another treatment modality that is deemed to be more appropriate for the participant's care.

All participants will be provided with a study information sheet that explains these general procedures (Attachment_44 in Table 3).

- (C) EXPERIMENTAL TASKS

The following experimental tasks will be split across sessions 1 & 2, and will be repeated during session 3 to assess intervention effects on a number of well-established psychological measurements related to cognitive and emotional function at several time points along the study progression.

(C1) EXPERIMENTAL TASKS IN THE BEHAVIORAL LABORATORY

Breath counting task

This task has been validated as an objective behavioral measure of mindfulness in four independent experiments with more than 400 participants. This measure is reliable and significantly correlated with self-reported mindfulness (Levinson et al. 2014). As in the previous study (Levinson et al. 2014), participants will be instructed to be aware of the movement of their breath and count their breaths from 1 to 9 repeatedly. With breaths 1–8 they will press one button, and on the nine breath they will press

another, measuring counting accuracy. Every ~90 s (60–120s range) experience sampling will probe state mind wandering and meta–awareness, respectively, with two 6-point Likert scales, "just now, where was your attention? (completely on-task/off-task)" and "how aware were you of where your attention was? (completely aware/unaware)." Participants will then be probed for their count.

Dot-probe Task

Using the Dot-Probe task we are going to measure negative emotion attentional bias. After presentation of a fixation cross in the center of the screen, participants are presented with 2 words from two categories (here: depression and neutral words). The position of the words is randomly chosen to be either above or below the location of the fixation cross. After a short duration, the two words disappear and a probe stimulus (here: < or >) appears in the location of one of the words. Participants are asked to press one key if the probe is < and another if the probe is >.

Autobiographical Memory Interview (Attachment_45 in Table 3)

In this task participants will be prompted with various words and will be asked to recall a specific event (lasting no more than one day) that happened in their past (within a timeframe of 6 months – 3 years before the date of the interview) related to each word, and verbally describe the event to the researcher. Then, each participant will be asked to rate each memory on a variety of dimensions (i.e., temporal distance, valence, personal significance, vividness, emotional intensity, approach vs. avoidance-related behaviors such as anxiety, motivation/difficulty engaging and unpleasant feelings while recalling. Lastly we will ask for the level of perceived controllability/uncontrollability regarding the ability to stop thinking about that memory when desired). Participants will be video recorded while reporting their memories. This task will serve as a means to quantify the nature of participants' autobiographical memory recall in an ecologically-valid manner, and will be later used during the MRI assessment.

Thought Fluency task/Free-association semantic task

In this task, subjects are given a cue and required to state the first word that comes to mind in response to the cue and repeat this process every 3s until a target number of response is reaches. Cues vary in level of self-reference, valence, type of thought elicited (i.e. FAILURE, FUTURE, etc.). In verbal fluency trials, the subject must list as many words as possible that fall within particular categories (e.g. begin with the letter "F"). Participants will be video recorded while completing this task.

Emotional movies task

We will use short emotional movies (total task duration 20 min) to assess moment-by-moment ratings of positive and negative emotions in the participants. We will specifically assess emotional reactivity; time to reach peak response and ability to recover the baseline emotional state. Specifically, the participants will be told that they will be viewing a positive and negative brief film clips lasting between 2-5 minutes in length, and answering questions at the end of the film clip. Film clips have been established as a valid and safe elicitor of emotion in laboratory settings and previously used by the P.I. (Gruber et al., 2008; 2011; Rottenberg, Ray & Gross, 2007). Positive film stimuli includes a variety of video clips and slides meant to induce particular positive emotions, such as compassion, pride, happiness, amusement, and enthusiasm. Examples of the video stimuli include the US Open tennis tournament depicting Andy Roddick winning the tournament, the figure skating Olympics depicting Sarah Hughes' gold medal victory, a clip about a boy named Trevor who helps homeless people in Philadelphia, a clip depicting heroism from the movie *Rudy.* The negative film stimuli include a variety of video clips and slides meant to induce particular negative emotions, such as sadness (clips from *Steel Magnolias, Dead Poets Society, Rocky, The Champ, and 21 Grams*) and fear (clips from *Taxi Driver* and *Trainspotting*). There will be a 60 second baseline before each film clip and a 60 second recovery period at the end of each film clip. At the end of

the film clip, participants will also self-report their emotions using the Affect Valuation Index (Attachment_20 in Table 3).

(C2) EXPERIMENTAL TASKS TO BE CONDUCTED IN THE MRI SCANNER

Rest task

In the rest task, participants will simply be asked to quietly relax for a period of approximately 6 minutes, and afterwards will be given a questionnaire to indicate the nature of their thoughts during this unconstrained task by allocating the approximate percentage of time they thought about various categories of thoughts (i.e. past-positive, past-negative, etc.).

"Narrative" vs "Experiential" task during autobiographical memory recall

Subjects will be exposed to a word probe signaling them to recall a specific autobiographical memory (that will have been previously assessed by the Autobiographical Memory Test). The participant will be asked to engage either: **(i) A Narrative Focus** mode, reflecting on what the memory means regarding their sense of self and their value as a person, allowing themselves to enter a train of thoughts or **(ii) An Experiential Focus** mode, monitoring their moment-to-moment experience in response to the memory being recalled (observing and monitoring their body response to the memories, thoughts and feelings that appear while trying to maintain an observers perspective in a non-judgmental, curious attitude without being trapped by the flow of thought). After each memory recall period subjects will be asked to complete a working memory task, a form of the n-back (1-back), in order to measure their ability to focus attention on an externally demanding task right after recalling self-related memories, which will make high-risk for depression participants more prone to enter a ruminative state.

Mood-induction task (administered during the acquisition of the anatomical scan)

Subjects will be asked to listen to a sad piece of music and to try and recall a time in their lives when they felt sad. The participants will be asked to experience as intensely as possible the feelings of the music and their memories for approximately 3-4 min. Similar music pieces as in Segal et al. 1999, Segal et al. 2006 and Joorman and Gotlib, 2008, will be used. This type of provocation (combining elements of music associated with sad mood and autobiographical recall) has been found to be effective in bringing on transient dysphoric mood states (Martin, 1990).

Self-Syllable Judgment Task

This task will be administered both pre- and post- mood induction. Participants will see self-directed statements about personality traits that vary in terms of valence (negative, e.g., 'ugly', 'unintelligent' vs. positive, e.g., 'pretty', 'intelligent') and they have to rate how much that adjective trait applies to themselves. As a control condition for this task, subjects will be asked to report the number of syllables of each personality trait word.

Post-scanning memory assessment

Right after the imaging session we will perform a memory test to assess whether participants can recall the information presented during the Self-syllable Judgment task. Subjects will also judge the emotional valence of each stimulus. This will allow us to measure selective memory biases for negative information, particularly during the "self" condition.

- (D) NATURALISTIC THOUGHT SAMPLING (Attachment_58 in Table 3)

These daily surveys will be administered 5x per day for 7-10 days immediately following session 1 and 8 weeks following session 2. The naturalistic thought sampling surveys are designed to estimate several factors characterizing the occurrence of spontaneous thoughts in real-world settings. In particular, we will estimate the frequency with which participants engage in spontaneous thoughts, the nature of the participants' ongoing activity and environmental context, and the nature of the content underlying one's thoughts. To assess these factors, the participant will receive a text message on five randomly-determined occasions between 10am and 10pm until they respond to 35 thought sampling probes (a minimum of 7 days, maximum of 10 days. Participants will have the opportunity to either ignore the text message or continue onto questions assessing various objective and phenomenological questions regarding their experiences immediately before the alarm sounded by clicking on the link to a questionnaire on the *Qualtrics* survey website, where participants will enter a unique, non-identifying subject ID each time. While response options for some questions will be discrete, other questions will be answered using a Likert scale (from strongly disagree to strongly agree) to gain more precision. Participants will be asked to complete the spontaneous thought task prior to and following their intervention period and intermittently throughout the intervention. During these daily thought samples, we will also ask participants, if convenient, to speak their current thoughts out loud for 60 seconds and record this using the Voice Memos app (or equivalent) on their phone. They will then send this recording to our womens.wellness@Colorado.EDU email account. These recordings are so that we can transcribe participants' thoughts and analyze thought content as another between-group outcome variable in the study.

The instruments comprising the test battery will be programmed into a laptop or desktop computer. Participants will read and respond to all tasks and questionnaires directly on the computer in individual testing sessions with a trained researcher. The researcher will closely monitor the participant's progress, reading aloud the instructions as each new experimental task is presented and providing assistance as needed.

- (E) *Physiological measurements and visual eye tracking*

We will passively record a number of physiological variables during subjects performance of some behavioral (*breath counting task*, *emotional movies* and *probabilistic reward task*) and all MRI tasks. These measures include (a) heart rate, (b) skin conductance, (c) pupil diameter, (d) eye gaze, and (e) respiration. These recordings will be entirely passive and non-invasive, and will not require any additional effort on the part of the participants (except for having sensors attached to one's hand for physiological recording). Physiological data will be recorded using the BioPac Acquisition system and the Siemens Physiological Monitor system. Visual eye tracking and pupillometry will be conducted using an integrated SR Research Eyelink eye-tracker. The eye-tracker does not record video of the participants. We include a more detailed description of the specific equipment and measures:

Eye tracking system: We will use an EyeLink 1000 system for use in MRI environments (SR Research Ltd., Kanata, Canada). This system uses a non-ferromagnetic optimized design, with a fiber optic camera affixed to the bottom of the MRI head-side projector screen. It provides a 1000 Hz binocular sampling rate, 0.01 RMS spatial resolution, and a 32 x 25 tracking range. Multiple data types can be output for statistical analysis, including: fixation, saccade, interest area (overlay on presented stimuli), and trial-based reports. In addition, eye gaze to pre-defined areas of the stimulus display can be used as task responses.

Physiological recording system: We will record physiological measures including ECG monitoring, respiration, pulse oximetry and electrodermal activity using the BIOPAC integrated system (BIOPAC Systems Inc., Camino Goleta, CA). All components are specially designed for use in the MRI environment. Pulse can be measured via photo plethysmographic methods sensitive to Blood Volume Pulse (BVP). The transducer is non-invasively taped to the participant's finger or toe and records continuous pulse and pulse rate data. Respiration can be measured via a respiratory effort transducer, which measures changes in thoracic or abdominal circumference that occur as the participant breathes. The transducer has an adjustable Velcro strap to comfortably fit a wide range of participants, and records continuous respiration rate and amplitude data. Electrocardiogram and electrodermal data can be measured via radiotranslucent leads and disposable electrodes non-invasively attached to the participant's chest and palm or foot, respectively. The MRI Smart Amplifier removes MRI artifact from the source physiological data, allowing continuous recording during fMRI acquisition. AcKnowledge software from Biopac is used for physiological data analysis.

- (F) Summary of the study timeline:

Phone screening: After reviewing the information acquired using the online screening form (see Recruitment Methods for an entire description of this step), potential participants will receive a phone call during their preferred hours with screening purposes to further to further determine eligibility (see Recruitment Methods for further details on this procedure).

Session 1 – Clinical Interview & Behavioral Tasks (Groups 1 and 2): The first laboratory visit will last approximately ~3-4 hours. The first laboratory visit will consist of a diagnostic clinical interview and, if deemed eligible following the clinical interview, behavioral tasks completed on a computer.

Online Questionnaires & Naturalistic Thought Sampling (Groups 1 and 2): Participants will then continue at home to perform online assessments for an additional hour, and complete the daily naturalistic thought sampling surveys.

Session 2 – Behavioral Tasks & MRI (Groups 1 and 2): Eligible participants will be asked to return to the laboratory to complete additional tasks and assessments. This portion of the study will last approximately ~3 hours. The visit will consist of tasks completed on a computer designed to measure cognitive and emotional processing, and an MRI assessment. The MRI assessment will last for approximately 1 hour. During the MRI assessment, the subjects will be performing a number of cognitive- emotional tasks inside the scanner while we assess their brain activity in response to these tasks. After the MRI session, participants will be sent a link to a ~5-10 minute online questionnaire in which they will be asked to make subjective valence ratings for each word they generated in the *Free-association semantic task.* In this questionnaire, participants will rate a total of 140 words using a sliding scale from very negative to very positive. Because these words are unique to each participant in that they are generated by the participant during the experimental session, we cannot provide a copy of the questionnaire here.

8-session MBCT intervention (Group 2): If subjects are assigned to Group 2, they will be asked to complete the 8-session intervention. The participant will be asked to complete 8 class sessions that will be administered online. The completion of the class modules will take approximately 2 hours per week and the participant will need to do basic homework exercises that may take approximately 15-30 minutes per day. Participants also will have access to a coach who will support their participation by phone and email contact to promote engagement in the online interventions and to troubleshoot any challenges. As outlined above, we will also ask the patient participants to answer a brief set of

questionnaires each week, representing a subset of those completed before the intervention (see Table 3: attachment_18 PANAS, attachment_25 FFMQ, attachment_26 EQ, attachment_36 SCS, attachment_38 BPI, attachement_42, PHQ9, attachment_58 naturalistic thought sampling questionnaire). This will allow us to assess the evolution in their symptoms and their mindfulness skills along the course of the intervention.

Session 3 – Behavioral Tasks & MRI (Groups 1 and 2): After the end of the intervention (or 8 weeks after Session 2 for Group 1), the participant will be asked to complete Session 3, which will take about ~5 hours. The visit will consist of the same laboratory tasks as in Sessions 1 and 2 completed on a computer, and an MRI assessment. The MRI assessment will last for approximately 1 hour.

Online Questionnaires & Naturalistic Thought Sampling (Groups 1 and 2): Participants will then continue at home to perform online assessments for an additional hour, and complete the daily naturalistic thought sampling surveys.

6-month followup phone Interview and/or questionnaires (for Group 2 only: LIFE and questionnaires):
Following the MBCT intervention, participants in group 2 will complete the Longitudinal Interval Follow-up Evaluation (LIFE, please see Attachment_10 in Table 3) via a phone interview to ascertain subsequent diagnostic status, again according to DSM-V diagnostic criteria. The LIFE provides a retrospective assessment of relapse and recurrence based on a semi-structured interview. Participants from groups 1 and 2 will be sent a link to a subset of questionnaires. Participants in group 1 will not undergo any follow up assessments.
Once every two weeks during the 6-month follow up period, we will ask the participants to answer a very brief questionnaire (attachement_42, PHQ9) to assess the evolution of clinical symptoms during this period.

IV. ABOUT THE SUBJECTS

For this examination, we will recruit a sample of 30 healthy control participants and 30 women with a previous history of MDD. Participants will be recruited from the patient population accessible to Prof. Dimidjian through the Clinical Research Evaluation Services and Training clinic (CREST) center that she directs at the University of Colorado, Boulder and by advertising in online local forums/bulletins associated with the Boulder/Denver Community Mental Health Center. In order to have greater access to potential participants, as in previous studies in our Labs, we will access Craigslist, the Buff Mail, local mental health centers and clinical service settings, libraries, cafeterias, bus stops, local transit and, eventually, newspapers, email distributions lists, and online posting. (See following section, Recruitment Methods, for further details).

Eligibility criteria for Group 2 (women with a past history of MDD) include the following INCLUSION criteria: (1) women who are not currently pregnant, (2) meeting criteria for prior depression (at least two episodes) and showing residual symptoms of depression (PHQ-9 score of 5-12), (3) not meeting criteria for a current active depressive episode (SCID criteria) (4) having access to internet and a smartphone with data plan, (5) ages 18-55 and (6) receiving no antidepressant/anxiolytic medication or under a stable regime of antidepressants/anxiolytics.

Eligibility criteria for healthy participants include the following INCLUSION criteria: (1) women that are not currently pregnant (2) do not meet criteria for prior or current depression (3) having access to internet and a smartphone with data plan and (3) ages 18-55.

Exclusion criteria for all participants include:

- Current diagnoses of: psychosis, bipolar disorder/maniac episodes, OCD, persistent antisocial behavior, severe developmental delay, or persistent self-injury needing clinical management or therapy, organic brain injury, substance misuse.

- Past diagnoses of psychosis, bipolar disorder/mania episodes or OCD.
- Use of marijuana equal or more than 4 days per week.

Additional exclusion criteria related to Magnetic Resonance Imaging safety requirements:
We will exclude participants who have metal or electrical equipment including:

• Non-removable metal piercing
• Tattoos on head or neck, an older tattoo with metal-containing inks, and/or permanent makeup (eyeliner).
• An implanted (internal) defibrillator or pacemaker
• Cochlear (ear) implant
• Some type of clips used on brain aneurysms
• An intrauterine device (IUD) that is not compatible with the MRI scanner
• An implanted infusion pump device like an insulin pump
• Implanted nerve stimulators
• Magnetic dental appliances or fillings
• Metal plates, screws, staples, joint replacement, and prosthetics.

Additional exclusion criteria for all participants include the following:
• Clear claustrophobic symptoms.
• Abnormal capability of performing the experimental tasks as they are designed and implemented (e.g., unable to read, unable to cooperate during fMRI examination, showing visual processing impairments that cannot be corrected using lenses or any significant impairments in the processing of auditory stimulation).

All subjects will be asked to read carefully the experiment procedure and give their written informed consent to participate in the study.

Several members of the key personnel involved in the current study have extensive experience with fMRI scanning procedures, as all of them have been involved in a large number of fMRI experiments in the past. All researchers and assistants involved in the MRI study are also asked to complete a quiz about safety precautions in the MRI environment. The full-time scanner technician employed at the Intermountain Neuroimaging Consortium (Center for Innovation and Creativity, Boulder, CO) has extensive experience and training with MRI research protocols involving procedures that are very similar to the ones described in this protocol.

V. VULNERABLE POPULATIONS

Our study does not involve vulnerable populations.

VI. RECRUITMENT METHODS

Only the principal investigators, co-investigators, or experienced researchers in Prof. Dimidjian and Prof. Wager's research laboratories will invite subjects to participate in the study. Investigators López-Solà and Andrews-Hanna are Research Associates in the Department of Psychology and Neuroscience (CU Boulder) and/or Institute of Cognitive Science. June Gruber is an Assistant Professor at the Department of Psychology and Neuroscience. Yoni Ashar, Sarah Hagerty and Natasha Hansen are graduate students in clinical psychology with experience in research and clinical work with depressed individuals.

Participants will be recruited from the local area, including Boulder and Denver metro areas, through referrals from community mental health centers, clinical settings, and local advertisements. Recruitment will be conducted primarily through the Clinical Research Evaluation Services and Training clinic (CREST) center, directed by Dr. Dimidjian. We plan to recruit participants by phoning a group of participants who have agreed to be contacted for future studies, and flyering in the CREST center and other area research and clinical centers. Additionally, participants will be recruited from announcement via electronic posting including, but not limited to, Craigslist, Buff Mail, and via flyers posted at local medical settings in which participants may be identified for prior depression. We may post flyers at local libraries, cafeterias, bus stops, local transit and, eventually, newspapers. Interested participants will be invited to write an e-mail to the research team. We may post flyers in local schools of the Boulder area to attract potential mothers of children and adolescents attending the schools. Schools have already given permission for this action to Dr. Nicole K. Speer, the operations director at the Intermountain Neuroimaging Consortium. We will also be putting recruitment blurbs in the Intermountain Neuroimaging Consortium (INC) recruitment handout and on the INC website as well as sending out recruitment blurbs to INC-related list servers. This will give us access to church and community group newsletters, which might be an important source of recruitment.

After receiving the e-mail from the potential participants, the research team will send them via e-mail the link to the brief online screening form (see Attachment_6 and Attachment_7 in Table 3, which include a complete but summarized description of the study and specific consent to participate. Also, as part of the screening procedure we will add the PDSQ questionnaire, Attachment_7 in Table 3, PDSQ, i.e., Psychiatric Diagnostic Screening Questionnaire, to ensure that patients are not currently showing symptoms of any mental health disorder) using CU's secure survey system provider, i.e., RedCap. The potential participants are explained the nature of the study, the potential risks, benefits, entirely voluntary participation and option of withdrawal at all times, and are asked to sign a consent form. Then, they answer a few screening questions and provide initial demographic and basic health-related information. The research team will then call potential participants over the phone to further determine eligibility. The phone call will involve a detailed assessment of the screening questions (see phone screening scripts for the high-risk women and healthy control women, Attachment_46 and Attachment_47 in Table 3) to confirm the existence of at least one previous depressive episode and absence of a current clinical episode. Please see the Data Management section below for a detailed explanation of the procedures applied to screening data collected using the brief online screening form.

At the beginning of the phone screening, participants will be informed of the nature of the questions, told how long the call is expected to take, and asked whether there might be a better time to answer the

questions. Participants will be informed that the questions will be used to further determine eligibility. If appropriate, participants who are not eligible based on the prescreening will be provided a list of local mental health referrals. Participants who are eligible based on the prescreening will be scheduled for an intake appointment at the Department of Psychology to complete consenting and further screening.

VII. COMPENSATION

Participants will be compensated for participation using a fixed schedule (calculated using a rate of $10/hour for behavioral tasks and $25/hour for MRI sessions). Specifically, during Session 1, participants will be compensated $10 for completing the SCID and $20 for the behavioral tasks. Participants will earn $40 for completing Session 2. We will provide an Amazon Gift Card for value of $25 to participants in Group 2 half-way through the intervention to provide a reward for their sustained efforts and to further motivate the participants to continue. For session 3, we will compensate all participants (Group 1 and 2) $50. After completing the set of at home questionnaires, all participants (Groups 1 and 2) will receive $55 ($20 for at home questionnaires + a $35 bonus for completion of the study). This compensation ($55) could take the form of a mailed check or a gift card or by scheduling an appointment at our Laboratory, depending on the preference of the participant. Participants in group 2 will receive a $25 Amazon Gift Card for completing the 6-month followup interview and questionnaires. **In total, participants in group 1 can earn up to $175 and participants in group 2 can earn up to $225.** A detailed description of the payment schedule is provided in the Consent Form for each group.

VIII. CONSENT PROCESS

Participants who pass the initial screening questions and agree to continue will be scheduled for an appointment to come to our clinical CREST center, where they will undergo a verbal consenting procedure explaining the study in much greater detail, as well as the details of the written consent (which they will also sign) regarding potential risks, benefits, study compensation, data management and confidentiality. Also all participants will be given a verbal explanation of the purpose and procedures that will be used, and will be reminded that their participation is entirely voluntary. Importantly, participants will also be informed that they can choose to omit any responses or withdraw from the study at any time. Participants will be asked to initial each page to signify understanding the materials and procedures. All of them will be given a chance to read the consent form and ask any questions. They will be reminded that there is no penalty for choosing not to participate, or from withdrawing their participation at any time. A description of the MRI procedures is included in the consent form, and all participants will be given a verbal description of the MRI screening and pregnancy forms.

IX. PROCESS TO DOCUMENT CONSENT IN WRITING

The consent will be documented (see attached consent forms). We are including 2 different consent forms for groups 1 and 2, respectively.

X. SPECIMEN MANAGEMENT

N/A

XI. DATA MANAGEMENT

Data obtained using the brief online screening form, acquired after the participant provides written consent to participate, will be stored in a database and will be treated following the same security procedures that will apply to the rest of data collected in the study (see below). The screening data will be stored in restricted-access servers, which will only be accessible to the graduate students involved in the study (listed above) and the principal investigators.

After conducting and receiving informed consent in person at the 1st laboratory session, the researcher will enter the subject's unique ID code onto all subsequent questionnaires and stimulus presentation programs. The user ID is linked to participant identity only through a master list stored in restricted-access servers and/or in locked filing cabinets in a locked room, to which only the investigators have access. The internet site which may be used for at-home tasks will require participants to log-in with this unique ID.

The hard copies of participant data/questionnaires will be stored in locked filing cabinets in a locked room, to which only the investigators have access. Furthermore, all electronic data will be stored on a private, password-protected hard drive or secure university-hosted online server accessible only to the PI or trained researchers in the lab.

Audio-recorded interviews and videos of "responses" will be temporarily stored on an encrypted hard drive and identified by subject ID. A written and de-identified transcript of the audio files and videos will be created and electronically stored with the other subject data (tasks and questionnaire data). Then, the audio-recordings and videos will be erased.

These procedures will minimize the risk of personal information being divulged to individuals who are not members of the research team.

We plan on retaining all the collected data indefinitely. We will ask the participants to give us permission to contact them in future studies from our Laboratory (see Participant Online Brief consent form, Attachment_6 and Attachment_7 in Table 3), which will involve retaining their identifier information.

The MBCT intervention website will be hosted at Noggin Labs for the study's duration, and will be secured using a firewall and password access, with a 128-bit level of SSL encryption. User passwords will be distributed to participants via email by the research team. The research team will store a file linking the passwords to participants' identity on a password-protected computer inside a locked laboratory in the Department of Psychology & Neuroscience. NogginLabs **will not collect any identifying information** from participants and will only require access to their numeric device ID. Passwords and their associated web access will be deleted from the study registry by the research staff at the close of this study or at the patient's termination or completion of the study, whichever is earlier. The study team will have administrative access to the website to monitor activity. Noggin Labs is experienced in managing confidential data using encryption and passwords.

Regarding one of the experimental tasks mentioned above, the Dot Probe task, we plan on releasing **de-identified** data (subjects performance of this task) to another institution, The University of Toronto, where two collaborators (Dr. Normal Farb and Dr. Zindel Segal) will analyze it (please see the two attached letters, in which our collaborators declare the agreement as to the characteristics of their collaboration, Attachment_48 and Attachment_49 in Table 3).

XII. WITHDRAWAL OF PARTICIPANTS

Research subjects may withdraw from participation at any time. Should a research subject choose to withdraw from either research session, she may do so immediately and without penalty. The participant will be compensated in the amount reflecting her time. Subjects will indicate at the time of consent whether or not they give permission for researchers to retain their data if they choose to withdraw.

In case that the participant feels uncomfortable due to claustrophobic symptoms or any other MRI-related environment issue, or in case she is not able to maintain a still position, she will be withdrawn from the MRI part of the study, considering both ethical and quality of brain data, but will continue to undergo the intervention procedure and the behavioral experimental tasks outside the scanner.

Importantly, during the scanning session the participant will always be able to communicate with the technician and the researchers via a microphone system and a squeezable pneumatic device that will be provided at the beginning of the MRI session. The participant will be instructed to press the device if she feels uncomfortable, which will signal to the technician to stop the scanning procedure and take her out immediately.

XIII. RISKS TO PARTICIPANTS AND MANAGEMENT OF RISKS

The potential risks associated with participating in this research are minimal.

Every member of the research team will be trained in standard regulations governing the conduct of human subjects research. Specific additional training regarding phone screening, clinical interviewing, and task assessments will also be implemented to ensure the safety and confidentiality of all research participants.

In addition to these important safeguards, we describe additional procedures we will use to minimize each of the identified potential risks described above.

Physical Risks

Depending on the individual's capacity there may be physical risks associated with the mindfulness or yoga practices in the MBCT sessions. We will ensure that patients stop any exercise or practice they think will be harmful to their health or well-being and not to engage in any practice at home that they think may cause harm.

Psychological, social, economic, and legal risks

There may be some psychological discomfort with (1) the knowledge that study personnel are reviewing participants' survey scores, health information, or other personal materials, and/or (2) the insight that may be gained from completing surveys and the group sessions. Study personnel will assure that participants understand the confidentiality measures taken in this study to protect them and their information. Participants will be invited at any time to share their concerns with the study co-investigators. Every precaution will be taken to protect personally identifiable information and avoid disclosure. In order to minimize psychological risk of harm, we will include detailed information about possible risks in the informed consent form and process. Participants will also be instructed that they are

free to not answer any questions they do not wish to answer on the questionnaires and during interviews, and that they may abort participation in the study at any time.

We have designed the assessment procedures to minimize burden on participants. We have ensured that there is no redundancy in measurement tools, with the exception of depression outcomes that are assessed both by self-report and clinical interview, which is standard in clinical research of this type. We also include a number of different assessment days to avoid exhaustion or boredom. Assessment appointments will be scheduled at times that are most convenient for participants.

MRI environment-related risks

The magnetic field of the MRI environment has the potential to cause burns or bodily injury if ferrous metal objects are implanted in the body, or if personal articles containing ferrous material are brought into the MR environment. Because we are excluding participants with contraindications for MR studies (e.g., metallic implants such as pacemakers, surgical aneurysm clips, or known metal fragments embedded in the body) using a standard screening form, the risk of damage due to implanted metal is low. Investigators and personnel of the MRI unit have extensive experience with standard safety precautions, including safety screening on paper and verbally by a trained technologist. These considerations minimize the risk of accident or injury in the MR environment. Although the risk of MRI to pregnant women is currently unknown (and is widely thought to be nonexistent), pregnancy is a standard exclusion criterion for MRI scanning. We will offer all participants in the fMRI study a free pregnancy test. Participants who decline this request will be asked to sign a document to acknowledge this.

Incidental and MRI findings

Each image will be reviewed by the technician and/or Co-Investigators for anomalies. We expect to observe at least one incidental finding in 42.9% of the scans, with 2.2% requiring further clinical action (Orme et al, 2010).

In the case of an anomalous finding in a brain image, the following procedure is followed:

1. The technologist and/or research personnel flag potential abnormalities.
2. The MRI technologist notifies the INC Director of Operations, the MRN Director of Research and Clinical Operations, and the P.I.
3. The scan gets queued to the radiologist worklist in COINS. All cases of suspected incidental findings are sent for formal neuroradiologic review at MRN.
4. Radiology reviews will be completed within 30 days.
5. The radiology review contains a written summary of the findings and classifies the referral status into one of these categories:

- No referral: The finding is not medically relevant and there is no need for follow-up with a physician.
- Referral: The finding shows something that needs to be brought to the attention of the participant's doctor.

6. INC staff, the MRN Director of Research and Clinical Operations and the PI will get an electronic copy of the radiology review (coded via URSI) as soon as the review is completed.
7. If a referral is recommended, the MRI technologist will contact the participant and explain that an unusual feature was observed in their scan and it was reviewed by a radiologist, leading to either a referral or a no referral recommendation. In the case of a referral, the technologist will

provide contact information for the MRN Medical Director in case the participant has questions prior to contacting his or her physician.

All cases reviewed will generate a formal radiology report, which is printed on letterhead and a copy of which is mailed to the participant.

Risks to privacy and confidentiality
Identifying documents will be de-identified and coded with a unique study ID number. Information will be stored confidentially in a locked file cabinet and in computer files protected by passwords and located in a secure facility. Access to information will be restricted on a "need to know" basis for this study. No information will be disclosed to others without written permission from the participant, except: 1) if necessary to protect the patient's rights or welfare; or 2) if required by law. Only aggregate, de-identified data will be reported. Data will be housed at CINC (Center for Innovation and Creativity, University of Colorado, Boulder) and archived for seven years and then destroyed by shredding or electronically.

Participating in this study will involve access to the REDCap websites – where the online surveys will be completed. The self-report surveys will be hosted by REDCap and will be secured using a firewall. All participants enter their responses to instruments using a study assigned ID, so that identifying data is never recorded at this stage. All data are accessed only by the study team who must provide a user ID and a password.

All information that directly identifies the subjects will be kept in a locked file cabinet, and separate from the research data, which will contain only the unique subject number. Because the UCB research co-Investigators may need to contact participants during the study, their phone number and email address will be stored in a locked file cabinet in Dr. Dimidjian's research office at CU Boulder. Only de-identified data will be used in publications.

XIV. POTENTIAL BENEFITS

All remitted patients will be receiving online MBCT (an empirically validated program) classes that may be beneficial for their mental/physical health. They will receive coaching support by a trained clinical graduate research assistant. Those assigned to the MBCT class may benefit from receiving an empirically validated program to prevent depression relapse. More generally, the information obtained from their participation in this study may help in the development of new therapies to prevent relapse following recovery and benefit others looking to help themselves in this way.

Additionally, participants will also have the option to receive a copy of their MRI brain scan (structural MRI only) on a DVD. Doing so will require signing an additional MRI release form (attachment 61) in which they agree to take ownership of this scan for personal use only

XV. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

We do not anticipate that participation in this study will have an impact on participants' privacy interests. Community member recruitment is open to participants with a range of mood and psychiatric experiences. Research participants will be undergoing the study at the Center for Innovation and Creativity (CINC, CU Boulder), where both the MRI scanner and the CREST clinic are housed. Participants entering the CINC are unlikely to be stigmatized, as this building also contains a variety of other services and laboratories.

XVI. MEDICAL CARE AND COMPENSATION FOR INJURY

This research investigation involves minimal risk. There are no provisions for medical care or compensation to research participants.

XVII. COST TO PARTICIPANTS

Community members will visit the CINC on several instances along the study progression. Parking is free at these locations, however the participant is responsible for his/her own transportation fees. The payment for participation is intended to help compensate for such fees. Also, a number of buses would allow participants to reach these centers easily.

XVIII. DRUG ADMINISTRATION

No drugs will be administered as part of this protocol.

XIX. INVESTIGATIONAL DEVICES

No investigational devices will be used in this protocol.

XX. MULTI-SITE STUDIES

N/A

XXI. SHARING OF RESULTS WITH PARTICIPANTS

Research results will not be shared with participants.

XXII. DISCLOSURE OF INVESTIGATORS

Dr. Dimidjian is on the advisory board Mindful Noggins, which is part of NogginLabs, a private company specializing in customized web based learning.