# The Impact of Mindfulness-based Cognitive Therapy on Neural Processing of Sadness Provocation and Depressive Relapse in a High-Risk Sample

by

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## Abstract

The current study sought to investigate the neural mechanisms underlying Mindfulness-based Cognitive Therapy (MBCT). Eighty-one remitted patients with a lifetime history of depression were recruited and randomly assigned to either MBCT or Cognitive Behavioral Wellbeing Therapy. Participants underwent functional MRI while completing a sadness provocation task at pre- and post-treatment. MBCT participants evinced lower activation of the posterior insula, a region implicated in body awareness, whereas MBCT relapsers evinced further MPFC deactivation, a region implicated in ruminative thinking. Moreover, it appeared non-relapsers exhibited stable brain responsiveness across time points, whereas relapsers tended to fluctuate. Findings indicate MBCT's emphasis on stabilizing behavioral symptoms extends to functional brain profiles, and the activation pattern in relapsers may reflect dissociation from current sensory experiences when confronted by dysphoric cues. Implications pertain to clinical practice in terms of the importance of regularly monitoring client progress throughout treatment and addressing the misapplication of mindfulness skills.

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# 1 Introduction

Adult-onset major depressive disorder (MDD) is a debilitating psychological condition primarily defined by a persistence of depressed mood or diminished interest and pleasure in most or all activities (American Psychiatric Association, 2013). Like various other diagnosable disorders, the onset and maintenance of MDD is marked by innumerable pernicious effects on psychological functioning and quality of life (Daly, et al., 2010; IsHak, et al., 2013), with as many as 63% of patients experiencing severe impairment (Rapaport, Clary, Fayyad, & Endicott, 2005), and many others at high risk of hospitalization, re-admission, and longer stay durations for non-psychiatric concerns (Prina, et al., 2015). Further compounding its detrimental impact on mental health is its high prevalence rate; lifetime rates of depression range from 4 to 10% worldwide (Kessler, et al., 2009), while afflicting approximately 4 to 7% of Canadians within the last year and 12% of them within their lifetime (Langlois, Samokhvalov, Rehm, Spence, & Gorber, 2012; Patten, et al., 2015). In view of these negative features, much effort has been devoted to the development of interventions that are capable of halting or reversing the natural progression of MDD and alleviating patient suffering.

In recent years, many pharmacological and psychological treatments have proven to be efficacious in mitigating acute-phase depressive symptoms (Cipriani, et al., 2009; Cuijpers, van Straten, Andersson, & van Oppen, 2008). Nevertheless, although the majority of patients appear to recover following the conclusion of treatment, many continue to exhibit residual depressive symptoms (Fava, Ruini, & Belaise, 2007) or fall prey to the high relapse and recurrence rates that emerge soon after remission. Relapse rates have been reportedly as high as 29% (Vittengl, Clark, Dunn, & Jarrett, 2007), and recurrence rates seem to increase over time, with as few as 15% of patients still in recovery after a 15-year period (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010). Thus, in spite of a reduction in depressive symptoms and their severity, other

psychological factors that are unresponsive to treatment must be exerting their influence over the course of MDD, and the identification of these factors is of clear clinical importance (Fava, Ruini, & Belaise, 2007).

## 1.1 Vulnerability Factors of Depression

Several candidate relapse vulnerability factors have emerged, including the high frequency of residual symptoms (Fava, Grandi, Canestrari, & Molnar, 1990; Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010; Ingram, Atchley, & Segal, 2011). Risk factors are comprised of demographic (e.g. gender, socioeconomic status) and clinical attributes (e.g. lifetime history of depression), whereas vulnerability factors consist mainly of psychosocial (e.g. lack of social support), developmental (e.g. childhood maltreatment), biological (e.g. decreased serotonin) and cognitive-emotional mechanisms (e.g. poor emotion regulation skills). In addition to their differential compositions, risks and vulnerabilities differ in terms of their explanatory value, as only vulnerability factors can provide substantive insight into the causative processes of depression (Ingram, Atchley, & Segal, 2011). For instance, studies of genetic predisposition can uncover the genotypes and phenotypes contributing to a depressive mindset, whereas the study of gender only informs us of the existence of a gender difference. By this reason, vulnerability inherently possesses more utility to the clinician than do risk factors.

Vulnerabilities can vary in their proximity to the onset of MDD, with *distal* factors, such as childhood abuse, occurring more remotely in time than *proximal* factors, such as current dysfunctional attitudes (Ingram, Atchley, & Segal, 2011). The nearness of factors to the MDD episode has important implications for clinical research and care. Studies of distal and proximal phenomenon have provided insights into differential facets of the disorder's etiology, revealing how inherited predispositions and early life experiences come to form proximal cognitive and personality susceptibilities (Hankin, et al., 2009); however, because proximal factors constitute

controllable immediate causes of depression, they are more amenable to psychological treatment where distal factors are not. To illustrate, Segal and colleagues (2006) reported that dysfunctional attitudes about oneself were associated with a higher likelihood of relapse, but subsequent treatment neutralized this relation.

## 1.2 The Two-Factor Model of Depression Vulnerability

Such findings led Farb, Irving, Anderson, and Segal (2015) to propose a two-factor model of depression vulnerability that underscored the pivotal role of proximal cognitive factors in instigating and sustaining depressive symptoms. According to the model, stress results not from negative life events per se, but rather from attention to and appraisal of said events. The cognitive mechanisms—attention and appraisal—influence each other in a cyclical manner; attention brings forth environmental features of a specific valence to be appraised, and the interpretation of that feature biases attention towards similar environmental cues. In the context of recurrent depression, these cognitive mechanisms become overly connected, with one easily influencing the other, further entrenching dysphoric attention and elaboration, which are also referred to as *fixation* and *rumination*, respectively. For instance, after arguing with a significant other, a person might attend to a specific aspect of the situation (e.g. “She said I was useless around the house”) that undergoes elaborative processing and becomes integrated into one’s self-concept (e.g. “I am useless. I can’t do anything right”), and biases attention towards mood-congruent information, only to further reinforce the negative self-schema (e.g. “I am worthless”). With each turn of the cycle, the individual becomes increasingly sensitized to negative environmental features to the extent that even minor stressors can trigger the fixation-rumination cycle, which in turn greatly enhances the risk of relapse and recurrence of depression.

The two-factor model was grounded in the empirical literature of proximal mechanisms underlying depression, and many of its claims and predictions have been informed by previous

behavioral and neuroimaging findings (Farb, Irving, Anderson, & Segal, 2015). Investigations of the neural underpinnings of these dysphoric cognitive mechanisms have linked fixation primarily to hyperarousal of the amygdala, anterior insula (AIC), and anterior cingulate (ACC), all of which constitute key regions within the task-switching Salience Network (SLN). In addition, fixation is associated with hypoarousal of the dorsolateral prefrontal cortex (DLPFC), a key region within the task-focused Executive Network (EXN). The amygdala, AIC, and ACC have been previously implicated in the redirecting of attention towards salient environmental cues (Vuilleumier, 2005), which dovetails with its apparent role in fixation, whereas the DLPFC has been implicated in regulating emotion via reappraisal (Etkin, Buchel, & Gross, 2015), as well as regulating activity from brain regions like the amygdala (Lieberman et al., 2007). With regard to rumination, underlying brain regions include the medial prefrontal cortex (MPFC)—a region implicated in self-referential processing (Lemogne et al., 2009)—that, along with the precuneus, posterior cingulate cortex, and angular gyrus, is a functional hub of the task-independent Default Mode Network (DMN), a neural network responsible for autonoetic awareness, awareness of one's emotions, and one's understanding of the emotions of others (Andrews-Hanna, 2012). Both the amygdala and the DMN neural hubs have been linked to depression (Buckner, Andrews-Hanna, & Schacter, 2008; Gotlib, Krasnoperova, Yue, & Joormann, 2004), and the DMN has also been linked to ruminative thinking (Zhu, et al., 2012), corresponding with the network's presumed internally directed function. However, perhaps the most telling finding is that, in non-depressed individuals, the DMN and other brain networks are fairly distinct from one another, whereas in formerly depressed individuals, these networks are commonly activated within the dorsal MPFC (Sheline, Price, Yan, & Mintun, 2010), representing the tight coupling of fixation and rumination at a neural level of analysis (Farb, Irving, Anderson, & Segal, 2015). The interfacing of networks in this region hinders one's ability to break the dysphoric cognitive

cycle, as fixation and rumination on salient affective cues prevents the individual from engaging in more adaptive responses for self-regulation (Farb, Irving, Anderson, & Segal, 2015).

## 1.3 Cognitive Reactivity and Risk to Relapse

Interestingly, many of these attentional biases and elaborative, dysfunctional thoughts are only predictive of relapse, and sometimes only detectable, when measured following inductions of depressed mood (Gibb, Beevers, & McGeary, 2013; Gotlib, et al., 2004), suggesting that dysphoric states elicit maladaptive cognitions. This causal relationship between mood and cognition has been termed *cognitive reactivity*, which is defined as the elicitation of maladaptive cognitions following a dysphoric state. Cognitive reactivity is a facet of rumination (Farb, Irving, Anderson, & Segal, 2015), a construct that has roots in Beck's theory of cognition (Beck, 1987), and a focal variable in diathesis-stress paradigms (Scher, Ingram, & Segal, 2005). Studies into this construct have yielded findings in support of its function as a vulnerability factor for relapse and recurrence (Scher, Ingram, & Segal, 2005) and its role as a malleable target for psychological interventions (Lau, Segal, & Williams, 2004). For instance, reactivity was found to be elevated in clients who were in the acute and remitted phases of depression (Ingram, Atchley, & Segal, 2011), and heightened in formerly depressed clients relative to those who had never been depressed (Lau, Haigh, Christensen, Segal, & Taube-Schiff, 2012). Moreover, the presence of such elevations was predictive of depressive relapse (Segal, et al., 2006). Altogether, such findings suggest that cognitive reactivity remains unaffected by current treatments for depression, perhaps due to their emphasis on thought content rather than thought processes. Left unchecked, reactivity continues to exert an insidious influence over the course of depression, even after once-prominent depressive symptoms have remitted.

In addition to its relation to clinical processes and outcomes, the neural underpinnings of cognitive reactivity have also been investigated with the use of brain imaging technology to

establish biomarkers and unearth their relation to the onset of MDD. Farb and colleagues (2011) compared remitted participants to healthy controls on a sadness-provocation task, whereby participants watched sorrowful film clips during a functional magnetic resonance imaging (fMRI) scan. The findings showed that remitted participants had more activity in the medial prefrontal cortex (MPFC) relative to healthy controls, and the divergent brain activity predicted increased rumination and depressive relapse, while normalized MPFC activity and increased reactivity of the visual regions were predictive of sustained remission. It was surmised that the former finding was in part due to compromised connectivity between the prefrontal regions such as the MPFC and limbic structures such as the amygdala (Heller, et al., 2009; Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007), whereas the latter finding was thought to stem from the allocation of one's attention to sensory experience rather than elaborating on dysphoric environmental stimuli. In sum, these findings have established the clinical significance of the neural response underlying cognitive reactivity, also referred to as *neural reactivity*, as a meaningful marker of relapse in its own right.

## 1.4 Relapse Prevention and Therapeutic Targets

Appreciating the apparent clinical utility of cognitive reactivity and other pathognomonic vulnerability factors, many have suggested that they be incorporated in any prophylactic intervention and in evaluations of treatment efficacy and effectiveness (Lau, Segal, & Williams, 2004). Two predominant approaches to relapse prevention have been to either institute first-line acute-phase treatments that produce enduring effects or to extend treatment regiments for months or even years to ensure proper recovery (Scher, Ingram, & Segal, 2005). Maintenance treatments produced from these approaches appear to be relatively efficacious (Hollon & Ponniah, 2010); however, they are also fraught with a number of shortcomings, the most important of which is that the design of acute-phase treatments may be suboptimal for persons in the remission-phase

of MDD, since these interventions were initially constructed to meet the needs of people in the acute phase (Fava, Tomba, & Grandi, 2007). With respect to antidepressant medication, Fava (2003) noted that their therapeutic benefits cease with the discontinuation of treatment, and proposed that the discontinuation of medication may paradoxically increase vulnerability to subsequent depressive episodes. As such, some have opted to convert acute-phase interventions into maintenance treatments or formulate new interventions altogether to meet the specific needs of remission-phase patients (Ingram, Atchley, & Segal, 2011).

In pursuing the latter avenue, some researchers have identified residual symptoms as a prognostic indicator of an imminent major depressive episode (Fava, Grandi, Canestrari, & Molnar, 1990). Fava and colleagues (Fava, 1999; Fava & Kellner, 1991) postulated that, while symptoms begin the process of remitting, they simultaneously become prodromal depressive symptoms that leave patients susceptible to relapse or the recurrence of depression—an occurrence known as the 'rollback phenomenon'. With such a powerful influence over the course of MDD, Fava and colleagues (Fava, Fabbri, & Sonino, 2002; Sonino & Fava, 2002) suggested that residual symptoms become a therapeutic target in maintenance treatments, and first sought to evaluate the efficacy of Cognitive Behavior Therapy (CBT), an empirically-supported acute-phase treatment, in this regard. One clinical trial compared standard CBT to clinical management, and demonstrated that fewer CBT participants reported depressive relapse or recurrence at the 2-year (15% vs. 35%), 4-year (35% vs. 70%), and 6-year follow-up assessments (50% vs. 75%) (Fava, Grandi, Zielezny, Canestrari, & Morphy, 1994; Fava, Grandi, Zielezny, Rafanelli, & Canestrari, 1996; Fava, Rafanelli, Grandi, Canestrari, & Morphy, 1998). A second longitudinal clinical trial evaluated the efficacy of CBT supplemented by aspects of lifestyle modification and Well-Being Therapy (CBWT) relative to standard clinical management. Lifestyle modification consisted of educating clients on maladaptive lifestyles and ways in which

such living habits can be altered to reduce stress and cultivate a healthier lifestyle (Fava, et al., 2004), whereas Well-Being Therapy focused on altering maladaptive beliefs and promoting behaviors that strengthen well-being constructs as described by Ryff and Singer's (1996) model of psychological well-being, such as autonomy, environmental mastery, and purpose in life (Fava, Rafanelli, Cazzaro, Conti, & Grandi, 1998). In comparison to clinical management, again fewer participants who had undergone CBWT reported depressive relapse or recurrence at the 2-year (25% vs. 80%) and 6-year follow-up assessments (40% vs. 90%) (Fava, Rafanelli, Grandi, Conti, & Belluardo, 1998; Fava, et al., 2004). Although the sample sizes of the foregoing trials were admittedly small (i.e. 20 participants per intervention), the favorable outcomes suggested that CBT-based approaches could be viable alternatives to maintenance antidepressant regimens.

Other researchers have taken a more cognitive approach in developing maintenance treatments, identifying protective cognitive skills on which to build a therapy. Teasdale and colleagues (2002) discovered that increases in the usage of metacognitive skills predicted a lower likelihood of depressive relapse, concluding that backsliding could be considerably reduced by changes in one's attachment to negative perceptions and not necessarily by restructuring thought content. Meanwhile, Fresco, Segal, Buis, and Kennedy (2007) reported that, following CBT, increases were seen in decentering, "the ability to observe one's thoughts and feelings as temporary, objective events in the mind" (p. 453), which in turn predicted lower relapse rates. Metacognition and decentering are clearly two valuable cognitive skills for patients to break away from the slippery slope of relapse, though a proper vehicle for delivery has to be employed for their effects to take root. Since these cognitive skills are promoted by engagement in mindfulness meditation (Feldman, Greeson, & Senville, 2010; Teasdale, et al., 2002), mindfulness practices became yet another potential alternative for preventing relapse.

## 1.5 Mindfulness and Neural Properties

Mindfulness is most commonly referred to as a state of mind where attention is purposely directed to the present-moment in a nonjudgmental fashion (Kabat-Zinn, 2005). Unlike other emotion regulation strategies that modify the attribution of meaning to salient emotional cues, mindfulness meditation does not restructure the content of perceptions, but instead alters one's relationship with them (Kabat-Zinn, Lipworth, & Burney, 1985). With regular practice, practitioners cease interpreting thoughts and feelings as accurate indicators of reality, and instead begin viewing them as passing mental events. These functional differences between regulatory strategies have also been reflected in their differential neural correlates. For instance, the reappraisal strategy emphasizes the reinterpretation of the meaningfulness of stimuli, and primarily recruits the dorsomedial prefrontal cortex (DMPFC), and bilateral DLPFC, ventral lateral prefrontal cortex (VLPFC), and posterior parietal cortex, all of which are regions implicated in cognitive control and self-regulation and have been shown to modify bilateral amygdala reactivity (Buhle, et al., 2013). In addition, seemingly similar strategies have also been associated with differing neural structures. Both reappraisal of environmental cues and distancing, which emphasizes a shift in perspective-taking in relation to stimuli (e.g. viewing it from a third-person perspective), are associated with greater recruitment of regions within the semantic system, such as the temporal and angular gyrus and inferior prefrontal cortex, and greater deactivation of SLN structures, such as the amygdala and parahippocampal gyrus. Nevertheless, only reappraisal was associated with the dorsal attentional system (Messina, Bianco, Sambin, & Viviani, 2015). Conversely, the neural correlates of mindfulness and acceptance strategies differ according to the degree of experience with meditation practices. More experienced practitioners exhibit extensive reductions in prefrontal cortices, including the MPFC, implicated in attention and working memory (Brefczynski-Lewis, Lutz, Schaefer,

Levinson, & Davidson, 2007), while novices exhibit decreased activation of the amygdala (Desbordes et al., 2012). Other studies have identified increased activation of various structures. Fox and colleagues (2014) meta-analyzed studies that had examined the neural correlates of mindfulness and other meditative techniques, and found eight brain regions were consistently activated across practices, including the somatosensory cortex and posterior insula, which underlie *interoception* or body awareness, as well as the ACC, middle cingulate, and orbitofrontal cortex (OFC), which are linked to self-regulatory functions. While there is some overlap in functional brain clusters between mindfulness and other emotion regulation strategies, the foregoing findings indicate that there are also unique neural signatures that may be reflective of differing psychological processes in dampening the intensity of emotional stressors.

## 1.6 Mindfulness-based Cognitive Therapy

Studies of mindfulness as an integrated component of psychological treatment have demonstrated its therapeutic effect in reducing vulnerability factors such as rumination and cognitive reactivity (Raes, Dewulf, Van Heeringen, & Williams, 2009; Ramel, Goldin, Carmona, & McQuaid, 2004), as well as in improving various cognitive abilities, such as attention and memory (Chiesa, Calati, & Serretti, 2011). Acknowledging the potential utility of mindfulness practices in relapse prevention, Segal, Williams, and Teasdale (2013) integrated mindfulness training with the cognitive-behavioral principles and practices of CBT, giving birth to Mindfulness-based Cognitive Therapy (MBCT). MBCT was designed as an 8-week group-treatment to instruct patients how to recognize their relapse pattern and teach them an assortment of meditative skills to be applied in their everyday life. At the outset of treatment, patients begin with yoga poses and the body scan, which is the practice of bringing attention to one's physical sensations; transition to seated meditations focusing on different emerging perceptions, such as thoughts or feelings; and finally end with learning the three-minute breathing space, an

abbreviated mindfulness skill that incorporates elements of the seated meditative steps in 3 minutes to bring an open awareness to the present moment. Throughout the treatment, homework is assigned and is a pivotal part of each patient's learning experience, but by the treatment's conclusion, patients are encouraged to create their own relapse prevention plan according to the demands of their lives**.**

Research on MBCT has been burgeoning since its inception, and much evidence is accumulating in support of its efficacy, especially for remitted patients with three or more lifetime major depressive episodes (Ma & Teasdale, 2004; Teasdale, et al., 2000). Piet and Hougaard (2011) conducted a review of the available randomized controlled trials of MBCT and found that, relative to placebo and waitlist control conditions, risk of relapse decreased by 34% in the MBCT group. More impressive still is that emerging evidence reported MBCT to be equally as effective as other efficacious active treatments. It has comparable effects to antidepressant maintenance treatments (Kuyken, et al., 2015) and cognitive psychological education, while outperforming the latter in the prevention of relapse for patients with higher vulnerability to MDD (Williams, et al., 2014). Moreover, MBCT reduces emotional reactivity to stressful situations (Britton, Shahar, Szepsenwol, & Jacobs, 2012), a relation mediated by mindfulness skills in remitted patients (Raes, Dewulf, Van Heeringen, & Williams, 2009). In contrast, Kuyken and colleagues (2010) reported an association between MBCT and higher cognitive reactivity, but higher relapse rates were not observed, suggesting that the treatment may have neutralized the negative ramifications of cognitive reactivity. Finally, a meta-analysis by Kuyken and colleagues (2016) analyzed individual patient data to determine the degree to which they influence the course of depression, and reported that MBCT participants had a reduced risk of relapse relative to waitlist control participants and participants from other active

interventions, and that MBCT had a greater impact on participants who reported more severe depressive symptoms at pre-treatment.

## 1.7 MBCT and Neural Mechanisms of Change

From these findings, Farb, Anderson, Irving, and Segal (2015) theorized that mindfulness emotion regulation and mindfulness-based interventions result in directing cognitive resources away from the aforementioned dysphoric fixation (SLN) and elaboration of external and internal cues (DMN), and instead deploys attention towards somatosensory and visceral cues, such as the breath, that are underlined by the somatosensory and posterior insular cortices, respectively. With continued practice, mindfulness practitioners begin to acknowledge the transitory nature of thoughts, feelings, and sensations, and gradually these perceptions begin to lose hold of their previous negative associations. According to the authors, efforts to self-regulate negative emotions in currently or formerly depressed individuals may trigger the dysphoric fixation-rumination cycle if the regulatory strategy involves analysis and elaboration of the content constituting dysfunctional beliefs. However, mindfulness is postulated to operate through alternative avenues. First, by focusing attention on body awareness through the posterior insula, activity is redirected away from self-referential regions of the DMN, and individuals become better able to refrain from elaborating on thought content. Second, the nonjudgmental attitude that one brings to mindfulness practices allows individuals to refrain from avoiding negative external or internal cues, instead allowing more adaptive engagement of such perceptions. These subcomponents are thought to effectively reduce both reactivity to and elaboration of negative cues, thus gradually decoupling the association between dysphoric fixation and rumination, and from a neural level of analysis, between the SLN and the DMN.

Although the neural profile underlying MBCT has yet to be investigated, other mindfulness-based interventions have garnered attention in this regard, revealing that the neural

properties of such interventions are associated with a number of specific brain regions also linked to the mindfulness state itself. Farb and colleagues (2007) examined the neural correlates of Mindfulness-Based Stress Reduction (MBSR), a specific intervention incorporating various mindfulness-based skills and practices, and reported an association between MBSR and diminished activity along the cortical midline, a structure implicated in self-referential thought. Furthermore, MBSR correlated with increased activation in the right lateral prefrontal cortex (LPFC) and visceromotor regions such as the insula and somatosensory cortex. Compared to waitlisted controls on a sadness-provocation task, the mindfulness-based intervention was again associated with decreased activity of the cortical midline (MPFC) and increased activation of the interoceptive brain regions (Farb, Anderson, Bloch, & Segal, 2011), suggesting that participants who underwent mindfulness training employed their newly developed skills when experiencing sadness that in turn reduced emotional reactivity. Finally, relative to a waitlisted control group, participants who had undergone MBSR exhibited strengthened functional connectivity between the right posterior insular cortex (PIC) and anterior insular cortex (AIC) during task-focused and task–independent fMRI activities and a reduction in DMPFC activity across conditions (Farb, Segal, & Anderson, 2013). In addition, those who had adhered with MBI practice guidelines showed greater activation of the PIC (Farb, Segal, & Anderson, 2013).

## 1.8 Aims and Objectives

Mindfulness practices and mindfulness-based interventions such as MBCT appear to be promising relapse-prevention tools and programs, but there are lingering questions to be addressed regarding the neural representation of relapsers and MBCT participants. First, neural signatures of relapse have only been investigated recently (Farb, Anderson, Bloch, & Segal, 2011), and as such, have yet to be replicated to ascertain whether the neural pattern evinced by relapsers resembles the relapse pattern predicted by the two-factor model of vulnerability to

depression. Second, despite great interest in this mindfulness-based intervention, only recently has its impact on cognitive reactivity (e.g. dysfunctional attitudes) been investigated (Kuyken, et al., 2010; Raes, Dewulf, Van Heeringen, & Williams, 2009), while its impact on neural reactivity still has yet to be explored. Research into this matter is paramount in uncovering the exact neuronal factors that underlie mindfulness and drive its prophylactic effects, and such neurobiological findings can also better inform cognitive-behavioral theories of psychopathology. Third, MBCT has yet to be compared to established psychological treatments like CBT, the intervention with the greatest evidence base for its efficacy in relapse and recurrence prevention (Cuijpers, et al., 2013).

While comparisons with placebo control groups can be informative in terms of unearthing the neural underpinnings associated with MBCT as a whole, such a research design is accompanied by several deficiencies that limit the meaningfulness of resultant findings (Parloff, 1986), including whether certain functioning brain regions are unique to the mindfulness training components of MBCT or simply the product of treatment features common to other psychological interventions. At this stage, MBCT should be more often compared to active treatments to identify its active ingredients, and comparisons with CBT specifically would be especially illuminating. As MBCT was founded on cognitive-behavioral principles of psychopathology and CBT, some elements of treatment are shared between the interventions; however, the addition of mindfulness is a distinct component of MBCT, and it has profound implications for the process in which relapse prevention is approached. For instance, while CBT appears to focus primarily on cultivating skills akin to cognitive reappraisal for alleviating depressive symptoms, MBCT instead emphasizes mindfulness strategies to ground participants in the moment and foster greater decentering and meta-awareness of one's perceptions. As aforementioned, previous investigations have differentiated the process and neural underpinnings

of these emotion regulatory strategies, but whether MBCT, which is compromised of more than mindfulness training alone, produces a post-treatment cortical representation that differs from or resembles that of CBT has yet to be explored.

The current investigation sought to identify the behavioral and neural mechanisms through which MBCT reduces the risk of MDD relapse and recurrence. We recruited a large cohort of fully remitted unipolar-MDD participants with a minimum of two past depressive episodes, who were randomly assigned to 8-week group-formatted Cognitive Behavior and Wellbeing Therapy (CBWT) or MBCT. Participants underwent pre- and post-treatment blood oxygenation dependent level (BOLD) fMRI scans while watching neutral and sad film clips and provided subjective sadness ratings at timed intervals. Clinically relevant self-report measures were used to gauge relapse status, frequency and severity of depressive and anxiety symptoms, interoceptive awareness, dysfunctional attitudes, and ruminative thinking style at quarterly assessments conducted over a 24-month follow-up period. Neural reactivity to stress was assessed using whole brain analyses and regions of interest established in prior research (Farb, Anderson, Bloch, & Segal, 2011; Farb, et al., 2010). Neural reactivity values, behavioral indices of cognitive reactivity, group assignment and relapse status will be inputted into Pearson correlation analyses to ascertain their relation to psychological constructs as measured through self-report. It was hypothesized that (1) hyperactivity of the MPFC—a region thought to underlie self-referential processes (Farb, et al., 2007)—would differentiate relapsers from non-relapsers, with relapsers showing greater activation relative to non-relapsers; (2) the MBCT group would evince increased activation of the rPIC, which has been associated with interoceptive awareness (Farb, Segal, & Anderson, 2013), from pre- to post-treatment; (3) the MBCT group would evince reduced activation of the mPFC from pre- to post-treatment, as the MPFC and rPIC are thought to be inversely related; and (4) the MBCT functional brain signatures would be distinguishable

from CBWT through differential activation of the rPIC and MPFC, with the MBCT group expected to show greater activation and deactivation of the rPIC and MPFC, respectively, relative to the CBWT group.

# 2 Method

## 2.1 Participants

### 2.1.1 Eligibility Criteria

Inclusion criteria consisted of the following: (1) 18 years of age or older; (2) lifetime diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV); (3) in remission phase of MDD; (4) total baseline Hamilton Response Scale for Depression (HRSD) scores equal to or below a score of 12; (5) endorsement of 3 items or less on the Structured Clinical Interview for DSM-IV (SCID) Module A; (6) have a family physician that must be willing to sign a release of information form; (7) have Ontario Health Insurance Plan (OHIP) coverage; (8) willing to be randomly assigned to either group treatment; and (9) ability to communicate and understand English at a grade 8 proficiency level. For item (2), dysthymia and as few as one chronic episode were deemed acceptable to meet the criterion.

Exclusion criteria consisted of the following: (1) current diagnosis of MDD according to the DSM-IV; (2) current diagnosis of an eating disorder, post-traumatic stress disorder, active substance abuse within the past 6 months or substance dependence, bipolar disorder (Type 1 only), and schizophrenia and other psychotic disorders; (3) current diagnosis of antisocial or borderline personality disorder; (4) presence of organic mental disorder or pervasive developmental delay; (5) past major depressive episodes (MDE) primarily due to a medical condition; (6) underwent electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS) within the past 6 months; (7) unwilling to be randomly assigned to either

group treatment; (8) have current contemplative practice (e.g. meditation, yoga); (9) had surgery or have condition (e.g. claustrophobia) that prevents participant from undergoing fMRI scanning; and (10) commencement or alteration of antidepressant medication regimen within the past 8 weeks. Participants on a pharmacological maintenance regimen were asked to keep medication doses stable for the 4 weeks preceding randomization.

### 2.1.2 Sample Size and Recruitment

A priori power analyses were conducted to determine the sample size required to ensure the detection of true effects using significance testing. The employed power program was customized for functional brain imaging research studies, incorporating parameters such as the alpha values for voxel cluster and height thresholds (Mumford, 2012), which were placed at 0.05 and 0.001, respectively. The desired power value was set at 0.80, and inputted effect sizes for individual brain regions and relapse predictors were derived from preliminary data obtained from 16 remitted MDD patients. Power analyses indicated that 35 participants per condition would be sufficient to detect the effect sizes of interest. To account for a presumed monthly attrition rate of 1% over the 24-month follow-up period, 5 participants were added to each condition, totaling a minimum sample size of 80.

Participants were recruited from outpatient clinics in the Greater Toronto Area that are affiliated with the Mood and Anxiety Program at the Center for Addiction and Mental Health (CAMH), as well as from the community through local advertisements. Prospective participants underwent a phone screener to determine their eligibility according to the aforementioned eligibility criteria, which were reassessed during the intake interview. 161 participants met criteria for inclusion and were randomly assigned to treatment condition (MBCT = 86, CBWT = 75) and therapist using block randomization, with a block size of 8 to match the number of participants allowed in any one session of MBCT or CBWT group-treatment. Age, gender, and

education were matched in both conditions. Of the 161 participants, 97 volunteered to undergo brain imaging at pre- and post-treatment, and after removing participants who had dropped out and had missing post-treatment imaging data (n = 12) or had attended less than four treatments sessions (n = 4), the final sample totaled 81 participants (MBCT = 46, CBT = 35). See Table 1 for further details on participant characteristics.

## 2.2 Clinicians

### 2.2.1 Therapists

Research *therapists* were recruited from the Cognitive Behaviour Clinic at CAMH. Therapists were included if they were mental health practitioners possessing a minimum of five years of experience with the administration of either CBWT or MBCT for preventing depressive relapse. Twelve therapists (six per psychological treatment condition) were recruited and assigned to the intervention matching their therapeutic orientation. All therapy sessions were audio recorded and used for treatment adherence rating at a later date.

### 2.2.2 Assessors

*Intake interviewers* and *follow-up interviewers* were research coordinators recruited from Dr. Zindel Segal's research lab. Interviewers were recruited if they held a Bachelor's degree or higher in psychology or any other scientific discipline. Interviewers were trained to administer the SCID, Hamilton Rating Scale for Depression (HRSD), and Longitudinal Interval Follow-up Evaluation (LIFE), and were blinded to treatment condition at every assessment point. Checks were used to determine the clinical interviewer's cognizance of the participant's treatment assignment.

Table 1

*Patient Characteristics in Percentages by Intervention and Relapse Status at Baseline*

| | MBCT (%) | CBT (%) | $\chi^2$ | *p* | Non-Rel. (%) | Relapsers (%) | $\chi^2$ | *p* |
|---|---|---|---|---|---|---|---|---|
| **Relapse Status** | | | .664 | .648 | | | - | - |
| Non-relapse | 78.26 | 80.00 | | | - | - | | |
| Relapse | 21.74 | 20.00 | | | - | - | | |
| **Gender** | | | .415 | .520 | | | 2.407 | .121 |
| Male | 30.23 | 37.14 | | | 37.70 | 17.65 | | |
| Female | 69.77 | 62.86 | | | 62.30 | 82.35 | | |
| **Education** | | | 3.924 | .141 | | | .864 | .649 |
| High School | 9.09 | 25.71 | | | 17.74 | 11.76 | | |
| College/University | 72.73 | 60.00 | | | 64.52 | 76.47 | | |
| Graduate/ Professional School | 18.18 | 14.29 | | | 17.74 | 11.76 | | |
| **Ethnicity** | | | 2.883 | .410 | | | 1.327 | .723 |
| Caucasian | 90.90 | 82.35 | | | 85.25 | 94.12 | | |
| Asian | 4.55 | 11.76 | | | 8.20 | 5.88 | | |
| Hispanic | 2.27 | 0 | | | 1.64 | 0.00 | | |
| Other | 2.27 | 5.88 | | | 4.92 | 0.00 | | |
| **Marital Status** | | | .764 | .682 | | | .580 | .748 |
| Married/Common-Law | 27.27 | 23.53 | | | 24.19 | 31.25 | | |
| Divorced/Separated | 20.45 | 14.71 | | | 19.35 | 12.50 | | |
| Never Married/ Single | 52.27 | 61.76 | | | 56.45 | 56.25 | | |
| **Income** | | | 4.053 | .542 | | | 7.675 | .175 |
| No Income | 0.00 | 2.86 | | | 0.00 | 5.88 | | |
| 0 – 29,999 | 20.45 | 22.86 | | | 22.58 | 17.65 | | |
| 30,000 – 69,999 | 25.00 | 37.14 | | | 33.87 | 17.65 | | |
| 70,000 – 99,999 | 22.72 | 17.14 | | | 16.13 | 35.29 | | |
| 100,000+ | 29.55 | 20.00 | | | 25.81 | 23.53 | | |
| Unknown/ Undisclosed | 2.27 | 0.00 | | | 1.61 | 0.00 | | |

Table 1 (continued)

*Patient Characteristics in Percentages by Intervention or Relapse Status at Baseline*

| | **MBCT** (%) | **CBT** (%) | $\chi^2$ | *p* | **Non-Rel.** (%) | **Relapsers** (%) | $\chi^2$ | *p* |
|---|---|---|---|---|---|---|---|---|
| **Employment** | | | 2.221 | .528 | | | 2.510 | .473 |
| Full-time | 60.00 | 51.51 | | | 54.39 | 62.50 | | |
| Part-time | 22.50 | 6.33 | | | 22.81 | 12.50 | | |
| Unemployed | 15.00 | 18.18 | | | 15.79 | 25.00 | | |
| Student | 2.50 | 9.09 | | | 7.02 | 0.00 | | |
| **Psychiatric Hospitalization** | | | .521 | .470 | | | .839 | .360 |
| Yes | 9.09 | 14.29 | | | 9.68 | 17.65 | | |
| No | 90.91 | 85.71 | | | 90.32 | 82.35 | | |
| **Family Depression** | | | 3.226 | .072 | | | .475 | .491 |
| Yes | 45.45 | 65.71 | | | 56.45 | 47.06 | | |
| No | 54.55 | 34.29 | | | 43.55 | 52.94 | | |

*Note.* CBT = Cognitive Behavioral Therapy, MBCT = Mindfulness-based Cognitive Therapy, Non-Rel. = Non-Relapse, $\chi^2$ = Pearson chi square.

## 2.3 Measures and Tasks

### 2.3.1 Clinical Interviews

The *Longitudinal Interval Follow-up Evaluation* (LIFE) interview (Keller, et al., 1987) is a semi-structured assessment of the severity and course of psychiatric disorders experienced over time using the criteria derived from the DSM-IV. It addresses several factors such as psychopathology, non-psychiatric medical illnesses, treatment, psychosocial functioning, and global health and psychological functioning. For the purpose of our study, we were only interested in the psychopathology scales concerning the assessment of mood disorders. The major affective disorders were rated on a 6-point scale, whereby increases in the frequency and severity of symptoms are paralleled by an increase in scores (e.g. 1 represents no residual symptoms and 6 represents severe symptoms meeting criteria for MDD). Inter-rater reliability estimates for diagnostic status ratings of the weekly course of affective episode disorders were very high (each item had an ICC equal to or above 0.90). Summaries of the course of affective episodes and of index episodes were also high in reliability, with most items obtaining an ICC of 0.81 or higher; however, two items, “partial remission status” and “>1 subsequent episode”, obtained ICCs of 0.55 and 0.59 respectively. Finally, although the LIFE was initially designed to be administered in 6-month intervals, it could also be used more frequently throughout the assessment period without any adaptations to be made. To obtain more precise assessments of the course of psychopathology, we administered the LIFE quarterly, and relapse was defined as the endorsement of enough criteria to warrant a current diagnosis of full or subthreshold MDD. A subthreshold diagnosis was defined as (1) endorsing fewer than five symptoms of MDD for a two-week period or (2) endorsing a sufficient number of symptoms that endured for more than

one week but less than two weeks. In either case, the symptom presentation must have been severe enough to cause distress and/or impairment in functioning.

The *Hamilton Rating Scale for Depression* (HRSD) (Hamilton, 1960) is a 17-item clinician-rated questionnaire measuring the number and severity of depressive symptoms experienced over a period of time. Items are rated on a 5-point Likert scale, and scores range from a point scale 0 to 68, symptom severity increasing as scores increase. Global scores below 9 indicate normal levels of symptoms, while scores above 19 indicate moderate to highly severe depressive symptoms. A recent review evaluated the reliability of HRSD and found that internal consistency was high (alpha = 0.784); inter-rater reliability was very high (ICC = 0.94, Pearson r = 0.94, Spearman r = 0.93, kappa = 0.81); and test-retest reliability was also very high (ICC = 0.93, Pearson r = 0.90), but was found to decrease as the duration of intervals between assessments increased (Spearman r = -0.74), though the exact magnitude of the drop in reliability was not specified (Trajković, et al., 2011). Another review confirmed the aforementioned findings, but directed criticisms at the HRSD's validity and individual item reliability (Bagby, Ryder, Schuller, & Marshall, 2004), which will be considered in the interpretation of scores and findings.

### 2.3.2 Self-Reports

The *SCID Overview and Demographics Information* form was used to collect demographic (e.g. gender, age, education) and clinical information (e.g. age of onset of first MDE) from the participant.

The *Body Awareness Questionnaire* (BAQ) (Shields, Mallory, & Simon, 1989) is an 18-item scale measuring awareness of one's normal bodily processes or interoceptive awareness. Items are rated on a 7-point Likert scale ranging from 0 (Not at all true of me) to 7 (Very true of me). Scores range from 18 to 126, and as the total BAQ score increases, so too does the level of

bodily awareness. Psychometric analyses with a student and community sample demonstrated that the BAQ had satisfactory internal consistency (alpha = .82) and high two-week test-retest reliability (*r* = .80) (Shields, Mallory, & Simon, 1989). In addition, moderate evidence of convergent and divergent validity was obtained for the BAQ, negatively correlating with measures of symptom reporting and positively with measures of self-focused attention to the body. Other studies of the BAQ have demonstrated that the BAQ moderated embodied cognitions, which are cognitions influenced by bodily processes (Häfner, 2013), and differentiated between practitioners and non-practitioners of yoga, a practice grounded in the body (Impett, Daubenmier, & Hirschman, 2006; Rani & Rao, 1994).

The *Beck Depression Inventory – II* (BDI-II) (Beck, Steer, & Brown, 1996) is a 21-item scale measuring cognitive and behavioral symptoms of depression, which are in line with DSM-IV criteria. Items are rated on a 4-point Likert scale ranging from 0 (Not at all) to 3 (Severely). As the total BDI-II scores increases, so too does the severity of reported depressive symptoms. Scores range from 0 to 63, with scores falling between 0-13, 14-19, 20-28, and 29-63 indicating minimal, mild, moderate, and severe depressive symptoms, respectively. Psychometric analyses with a psychiatric outpatient sample yielded very high internal consistency (alpha = 0.92), 1-week test-retest reliability (r = 0.93), and strong convergent validity, as evidence by the positive correlation between the BDI-II and the HRSD (*r* = .71). The BDI-II is comprised of two underlying factors: an affective component (e.g. self-criticalness, worthlessness) and a somatic component (e.g. anhedonia, concentration difficulties). Depression and other psychiatric groups differed on their total obtained scores, with the depression group scoring higher on the BDI than the others. A meta-analytic study of the BDI-II's psychometric properties determined that the scale demonstrated satisfactory test-retest reliability (r = .75) and internal consistency (alpha = .893) (Erford, Johnson, & Bardoshi, 2016). Furthermore, the BDI-II demonstrated good

convergent validity, as it was shown to correlate with a number of other well-established measures of depressive symptoms, including the Center for Epidemiological Studies-Depression (CES-D) and Hamilton Depression Inventory (HAM-D). Finally, the scale evinced satisfactory diagnostic validity, as it attained an estimated percentage of accurate classification of approximately 80%.

The *Dysfunctional Attitudes Scale* (DAS-17) (Weissman, 1979; Weissman & Beck, 1978) is a 17-item item scale measuring dysfunctional attitudes about the self. Items are rated on a 7-point Likert scale, and total DAS-17 scores range from 17 to 119, with increases in total score representing an increase in number and severity of dysfunctional attitudes. Confirmatory analyses indicated the DAS consisted of two subscales: one measuring perfectionism and performance evaluation (PPE) and the other measuring dependency (DE) (de Graaf, Roelofs, & Huibers, 2009). Total score, PPE, and DE were moderately correlated with depression severity (Pearson $r = .61$, .51, and .60, respectively), were able to significantly distinguish between depressed and non-depressed participants ($p < .001$), accounted for 25% of total variance in depression scores. Both subscales correlated moderately with one another and a one-factor model was also found to be sufficient to explain the factor loadings in confirmatory factor analyses (also supported by Moore, Fresco, Segal, and Brown, 2014), suggesting that the use of a total DAS score is an acceptable measure of overall dysfunctional thinking. The DAS Version A, an abbreviated form of the full 100-item DAS and from which the DAS-17 was constructed, attained high parallel-form reliability ($r = 0.83$) with the DAS Version B, an alternate abbreviated DAS measure, and the test-retest reliability (4- to 6-week period) for the complete DAS was moderately high (Oliver & Baumgart, 1985).

The *Ruminative Response Scale* of the *Response Style Questionnaire* (RSQ-R) (Butler & Nolen-Hoeksema, 1994; Nolen-Hoeksema, 1991) is a 22-item subscale measuring the frequency

of ruminative coping, an emotion regulation strategy in which the focus of one's thoughts are centered around one's emotions and their causes and consequences. Items are rated on a 4-point Likert scale ranging from 0 (Almost never) to 3 (Almost always). Scores range from 0 to 66, and as the total RSQ-R score increases, so too does the level of bodily awareness. Psychometric analyses of the scale have indicated that the RSQ-R has satisfactory internal consistency (alpha = .89) (Kasch, Klein, & Lara, 2001), and moderate evidence of predictive and convergent validity (Butler & Nolen-Hoeksema, 1994; Nolen-Hoeksema, 2000). Other studies have also reported that the RRS yielded a 2- to 3-month test-retest reliability coefficient of .56 in a sample of inpatients diagnosed with MDD (Kuehner & Weber, 1999), and a one-year test-retest coefficient of .62 in a community sample (Nolen-Hoeksema, 2000).

The *Beck Anxiety Inventory* (BAI) (Beck, Epstein, Brown, & Steer, 1988) is a 21-item scale measuring cognitive and behavioral symptoms of state anxiety. Items are rated on a 4-point Likert scale ranging from 0 (Not at all) to 3 (Severely). As the total BAI score increases, so too does the severity of reported anxiety symptoms. Scores range from 0 to 63, with scores falling between 0-7, 8-15, 16-25, and 26-64 indicating minimal, mild, moderate, and severe symptoms of anxiety, respectively. Psychometric analyses with a psychiatric outpatient sample yielded very high internal consistency (alpha = 0.92) and 1-week test-retest reliability (r = 0.75) and two underlying factors ("somatic symptoms" and "subjective anxiety and panic symptoms"). Anxiety and other psychiatric groups differed on their total obtained scores, with the anxiety group scoring higher on the BAI than the others. Other studies conducted on the validity and reliability of BAI scores have demonstrated high internal consistency for psychiatric and non-psychiatric groups alike, while test-retest reliability is higher for psychiatric groups than non-psychiatric groups (de Ayala, Vonderharr-Carlson, & Kim, 2005). BAI scores correlated moderately with

other established measures of anxiety (Beck & Steer, 1991; Fydrich, Dowdall, & Chambless, 1992), suggesting moderate evidence of convergent validity.

### 2.3.3 Sadness-Provocation Film Task

While undergoing fMRI scanning at pre- and post-treatment, participants were be asked to attend to four sets of film and television clips. The four sets of clips were selected from a total set of eight, of which four were sadness inducing and the remaining four were neutral. The sadness film clips were taken from *The Sixth Sense* (1999), *The Champ* (1979), *Stepmom* (1998), and *Terms of Endearment* (1983), while neutral clips were taken from gardening and woodworking television shows. Sets were placed into one of two task runs, each run containing one sadness and neutral set. Individual clips were shown in 50-second blocks separated by fixed intervals of 30 seconds. During the interval period, participants reported their subjective feelings of sadness on a 5-point Likert scale (1 = Not at all, 7 = Very much) using an fMRI button box provided by the scanning technician. Sadness ratings were collected at pre- and post-treatment, and presented film sets were counterbalanced across time points for each intervention group.

## 2.4 Training Protocol

### 2.4.1 Mindfulness-based Cognitive Therapy (MBCT)

MBCT (Segal, Williams, & Teasdale, 2013) is a manualized 8-week group intervention that integrates Buddhist principles and practices (e.g. mindfulness meditation) with those of traditional CBT for the purpose of preventing depressive relapse and recurrence. It works to this end by teaching patients to nonjudgmentally focus their attention on the present moment and to approach arising thoughts, feelings, and sensations in a curious, nonreactive, and accepting manner. Throughout the weekly 2-hour sessions, patients gradually realize that perceptions are not truths about reality but rather are passing events in the mind, which in turn loosens the grip

of automatic negative perceptions over their wellbeing. Patients are taught several meditative skills (e.g. body scan, seated meditation), and are regularly assigned homework (30-60 minutes daily) to bring mindfulness to their everyday lives.

### 2.4.2 Cognitive Behavior and Wellbeing Therapy (CBWT)

CBWT (Beck, Rush, Shaw, & Emery, 1979) was converted from the manualized individual intervention into a group-format treatment that includes components of lifestyle modification and well-being therapy (Fava, Rafanelli, Grandi, Conti, & Belluardo, 1998). It is conducted weekly in 2-hour sessions over the course of eight weeks, and is focused on guiding patients in adjusting irrational beliefs and dysfunctional attitudes that impair wellbeing, making adaptive lifestyle changes to minimize social-environmental stressors, and adopting behaviors meant to improve wellbeing and personal growth. CBWT contains no mindfulness components, but patients in this condition were equivalently assigned daily homework exercises (30-60 minutes in daily). There are no discrepancies in allotted treatment duration between MBCT and CBWT.

## 2.5 Procedure

Prospective participants were administered a phone screener and an intake interview to determine their eligibility for the study; at intake, participants underwent the SCID and HRSD, and completed the fMRI screening form. Eligible participants were scheduled for fMRI scans, where they completed the sadness-provocation task, as well as other tasks as part of a larger longitudinal study. Symptom and resilience questionnaires, including the DAS and BAI, were completed outside the scanner. Participants were then randomly assigned to the MBCT or CBWT groups and attended weekly treatment sessions for the following 8 weeks. At post-treatment, participants were scheduled for their second fMRI scanning appointment at the same

location, and followed the same protocol observed at pre-treatment. Participants were then assessed at follow-up sessions in quarterly intervals over a 24-month period. At each follow-up, assessors asked participants to complete additional batteries of questionnaires and administered the LIFE and HRSD to ascertain relapse status.

## 2.6 Brain Imaging

### 2.6.1 Image Acquisition

The MRI system used was the Siemens Trio 3.0-Tesla scanner with slew rate of 400 T/m/s and a 12-channel asymmetric gradient head coil, which is housed at the Rotman Research Institute at Baycrest (Toronto, ON, Canada). There were two experimental sessions in which brain imaging data were collected (pre- and post-treatment). During each session, 2 runs of 434 functional volumes were collected, for a total of 868 volumes per session. The 3D magnetization-prepared rapid acquisition gradient echo planar pulse sequence was used to construct T1-weighted structural brain images (TR = 2000 ms; TE = 2.63 ms; matrix = 256 x 160; field of view = 256 x 256; slice thickness = 1 mm thick; 160 oblique axial slices; total acquisition time = 6.5 min). Functional images were constructed from the blood oxygenation level-dependent (BOLD) fMRI signal using T2*-weighted gradient-echo echo-planar image pulse sequences (TR = 2000 ms; TE = 2.63 ms; flip angle = 270 degrees; acquisition matrix = 64 x 64; field of view = 200 mm; voxel resolution = 3.1 x 3.1 x 5 mm; 30 slices in oblique axial orientation).

### 2.6.2 Preprocessing

Statistical Parametric Mapping (SPM12) was used to preprocess the obtained BOLD fMRI signals. Images were realigned to correct for motion, and segmented using template tissue probability maps (International Consortium for Brain Mapping) for gray matter, white matter,

and cerebrospinal fluid. Images were also normalized to fit a standardized brain space, with voxels resampled to 3x3x3 mm in size (Montreal Neurological Institute or MNI) and then spatially smoothed (6 $mm^3$ full-width at half-maximum Gaussian kernel).

## 2.7 Data Analyses

Prior to fMRI and relapse analyses, participants were removed from the dataset if they had failed to attend a minimum of four intervention sessions or dropped out of the study prior to undergoing the post-treatment brain scan.

### 2.7.1 Self-Report Measures

To measure reactivity to sad mood provocation, behavioral sadness reactivity scores were computed as the difference in sadness ratings between the Sad and Neutral film conditions. As a manipulation check of the sadness provocation paradigm, we investigated whether sad film clips were associated with great sadness ratings than neutral film clips using a one-way ANOVA. In addition, change scores in behavioral sadness reactivity and self-report measures were computed by calculating the difference between scores at pre- and post-treatment, with positive and negative scores reflecting an increase and decrease across time, respectively.

To determine whether participant groups differed at pre-treatment, demographic and clinical factors, baseline self-report measures, and baseline sadness ratings were subjected to a between-subjects three-way mixed-model ANOVA, with intervention, time, and relapse status as the independent factors. In addition, change scores were submitted to Pearson correlations to examine their association with the foregoing independent factors.

### 2.7.2 Imaging Analyses

For *first level* analyses, participant data were inserted into a general linear model. Task-specific boxcar stimulus functions were combined with canonical hemodynamic response

functions to model signals from the sadness-provocation and neutral film tasks as separate experimental regressors. Six motion regressors obtained from the realignment step as well as mean white matter and cerebrospinal fluid values were included in the first level model as nuisance regressors.

For *second level* analyses, the first-level sadness- and neutral-condition regressors were contrasted and inserted into analyses as dependent variables to detect brain activity underlying sadness reactivity. Analogous to the behavioral data, neural sadness reactivity was operationalized as the contrast between Sad and Neutral film clips. To characterize sadness reactivity, reactivity brain maps for each participant were constructed at both the baseline and post-intervention time points using t-test contrasts and were subsequently analyzed using additional t-test contrasts designed to evaluate main and interaction effects, with imaging time point, treatment condition, and relapse status as the independent factors. In addition, conjunction analyses were employed to identify functional brain clusters common to participants across intervention, time, or relapse status. The probability maps were thresholded for ROI and whole brain analyses at $p < .05$ and $p < .005$, respectively, while cluster thresholds were set at $k = 20$ for both analyses. According to the Montre Carlo simulation ran with the AlphaSim toolbox for SPM, the probability of finding a cluster size of 20 by chance is just under 5%, given the height threshold of $p = .005$.

A priori gray matter masks for the right posterior insular cortex (rPIC) and the medial prefrontal cortex (MPFC) were produced to evaluate how these ROIs were recruited among imaging time points, treatment conditions, and relapse statuses. Participant signals from the *a priori* ROIs in each examined condition were averaged into median signals using the REX toolbox for SPM. These values were subjected to the t-test procedure described above. To evaluate the overall functional brain pattern in each examined condition, whole brain analyses

were also conducted. For these post hoc evaluations, cluster corrections to control the false-discovery rate were adjusted to minimize the increased familywise error from the multiple whole brain comparisons. Finally, functional brain cluster signals were submitted to exploratory Pearson correlation analyses to ascertain their relation to specific self-report change scores.

# 3 Results

## 3.1 Clinical Effects of MBCT and CBWT

Of the total sample, 17 participants (MBCT = 10, CBWT = 7) relapsed over the course of the study. Demographic, clinical, and baseline self-report variables were evaluated for their relation to intervention group and relapse status (see Tables 1 and 2). The MBCT and CBWT groups did not differ in number of relapsers, and intervention and relapse status groups did not differ on demographic variables.

In regards to clinical factors, no main and interaction effects of intervention or relapse status were detected in the number of past episodes, time since most recent episode, or duration of the most recent onset. However, some baseline differences were found. A trending main effect of intervention was detected for family history of depression, $F(1,75) = 4.10$, $p < .06$, with higher rates in CBWT participants than MBCT participants (68% vs. 40%). Other statistically significant indicators suggested more severe histories in the CBWT group, including elevated higher rates of suicide attempts, $F(1,75) = 4.16$, $p < .05$ (23% vs. 4%), and psychiatric hospitalizations, $F(1,75) = 5.01$, $p < .05$ (25% vs. 6%).

Two interaction effects of intervention by relapse status were also detected. First, for psychiatric hospitalizations, $F(1,75) = 7.73$, $p < .01$, MBCT non-relapsers reported more hospitalizations than relapsers (11% vs. 0%), whereas CBWT relapsers reported more

Table 2

*Intervention and Relapse Status in Analysis of Demographic, Clinical, and Baseline Self-Report Measures*

| | **Intervention** | | | **Relapse Status** | | |
|---|---|---|---|---|---|---|
| | MBCT *(M±SD)* | CBT *(M±SD)* | *F* | Non-Relapse *(M±SD)* | Relapse *(M±SD)* | *F* |
| **Relapse** | -.57 ± .83 | -.60 ± .81 | .04 | - | - | - |
| **Demographic** | | | | | | |
| Age | 40.61 ± 12.04 | 37.11 ± 12.65 | .53 | 39.89 ± 12.47 | 36.06 ± 11.80 | 1.15 |
| **Clinical** | | | | | | |
| Age of Onset of First Episode | 21.33 ± 10.46 | 19.71 ± 8.59 | .29 | 20.17 ± 8.68 | 22.18 ± 12.70 | 1.11 |
| Age of Onset of Most Recent Episode | 38.32 ± 12.09 | 33.85 ± 11.52 | .87 | 36.90 ± 11.88 | 34.47 ± 12.50 | .42 |
| Duration of Most Recent Episode | 38.53 ± 53.78 | 50.61 ± 70.06 | .91 | 44.18 ± 57.17 | 41.65 ± 74.27 | .00 |
| Suicide Attempts | .07 ± .25 | .20 ± .41 | 4.16* | .13 ± .34 | .12 ± .33 | .01 |
| Episodes | 4.32 ± 2.73 | 3.53 ± 1.85 | 3.41 | 4.08 ± 2.36 | 3.59 ± 2.58 | .93 |
| **Baseline Self-Report** | | | | | | |
| BAQ | 78.43 ± 16.91 | 79.03 ± 17.13 | .04 | 78.36 ± 16.20 | 79.94 ± 19.80 | .13 |
| BAI | 5.72 ± 5.17 | 7.09 ± 6.27 | .23 | 5.88 ± 5.46 | 7.94 ± 6.33 | 1.50 |
| BDI-II | 6.20 ± 5.67 | 6.57 ± 5.06 | .03 | 5.92 ± 5.45 | 8.00 ± 4.95 | 1.86 |
| DAS | 50.80 ± 14.19 | 55.74 ± 21.27 | 1.55 | 53.14 ± 18.33 | 52.18 ± 15.32 | .01 |
| HRSD | 2.02 ± 2.76 | 2.60 ± 2.19 | .93 | 2.25 ± 2.67 | 2.35 ± 2.00 | .04 |
| RSQ | 43.83 ± 13.91 | 46.40 ± 12.71 | .53 | 43.75 ± 12.99 | 49.41 ± 14.30 | 2.40 |

*Note.* * $p < .05$, ** $p < .01$; CBT = Cognitive Behavioral Therapy, BAI = Beck Anxiety Inventory, BAQ = Body Awareness Questionnaire, BDI-II = Beck Depression Inventory – Version 2, DAS = Dysfunctional Attitude Scale, HRSD = Hamilton Rating Scale for Depression, MBCT = Mindfulness-based Cognitive Therapy, RSQ = Response Style Questionnaire.

hospitalizations than non-relapsers (12% vs. 7%). Second, for onset of first depressive episode, $F(1,73) = 4.01$, $p < .05$, MBCT non-relapsers reported an older age of onset than relapsers (21.9 vs. 19.4 years), whereas CBWT relapsers reported an older age of onset than non-relapsers (26.1 vs.18 years). Intervention group and relapse status did not significantly differ in pre-treatment BAQ, BDI-II, BAI, DAS, HRSD, and RSQ-R scores.

Scores on the BDI-II, HRSD, and BAI indicated that most participants were experiencing minimal levels of depression and anxiety at baseline, and HRSD scores were below clinical cutoffs. DAS and RSQ-R scores indicated that most participants also exhibited minimal dysfunctional attitudes and ruminative thinking styles. Mixed model (Intervention Group x Time x Relapse Status) ANOVAs conducted for each self-report measure indicated that BAI scores, $F(1,77) = 6.91$, $p < .05$, and BAQ scores $F(1,77) = 8.10$, $p = .006$, increased with time. A three-way interaction effect was significant for HRSD scores, $F(1,77) = 6.014$, $p < .05$, such that MBCT relapser, non-relapser, and CBWT non-relapser scores all decreased with treatment, whereas CBWT relapser scores increased over time. However, all HRSD scores at post-treatment remained within the normal to minimal symptom range.

## 3.2 Behavioral Correlates of Sadness Provocation

As a manipulation check of the sadness provocation paradigm, we investigated whether sad film clips were associated with greater sadness ratings than neutral film clips. A significant effect of film type was observed, $F(1, 34) = 139.99$, $p < .001$, suggesting that the sad films, $M = 2.94$, $SE = 0.16$, 95%, CI = [2.62, 3.26], evoked significantly greater reported sadness than the neutral films, $M = 1.18$, $SE = 0.04$, 95%, CI = [1.09, 1.26]. We also examined baseline sadness ratings and behavioral sadness reactivity scores, as indexed by difference scores of sadness ratings between sad and neutral film clips, as a function of intervention and relapse status with a mixed-model ANOVA. There was no main effect of intervention group or relapse status, nor was

there an interaction effect between the two.

## 3.3 Neural Correlates of Sadness Provocation

Sadness reactivity was associated with midline clusters of cortical activation (see Figure 1a and Table 3), which included the (1) bilateral cuneus, precuneus, and posterior and middle cingulate (BA 7/23/30); (2) bilateral anterior cingulate, medial orbitofrontal, middle frontal, and medial and lateral superior frontal regions (BA 10/32/34/46); (3) bilateral thalamus, dorsal striatum, insula, and inferior frontal cortices (BA 25/47/48/45); and (4) bilateral middle temporal region (BA 20/21). Reactivity was also associated with lateral clusters of activation, which included the (5) left and (6) right angular, supramarginal, and middle temporal regions (BA 39/40/41/22); and (7) right angular, supramarginal, and middle and superior temporal regions (BA 21/22/39/40/41/42/48).

Sadness reactivity also evoked neural deactivations (see Figure 1b and Table 3), which included the (1) bilateral anterior and middle cingulate cortex (BA 24); (2) left pars triangularis of the inferior frontal region (BA 45); (3) left middle and superior frontal region (BA 6/8); (4) right thalamus (BA 27); and (5) a widespread bilateral network enveloping the insula (BA 48), extending laterally to the superior temporal (BA 22) and somatosensory cortices (BA 2/3/4), and terminating posteriorly in the precuneus (BA 7).

## 3.4 Effects of Relapse Status on Neural Reactivity

The neural correlates of relapse vulnerability were examined by evaluating the main effect of relapse status, collapsing across time and intervention groups (see Table 4 for further details).

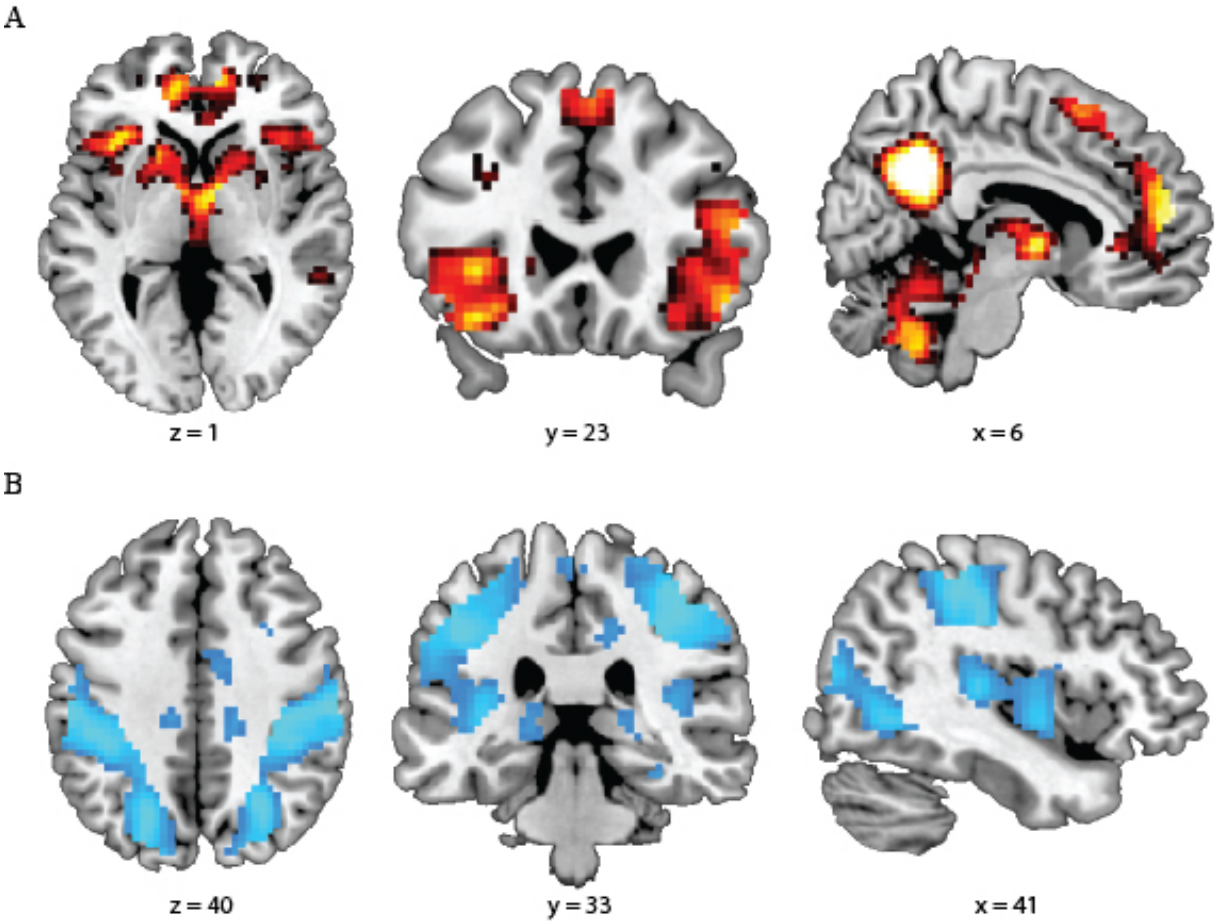


*Figure 1*. Differences in regional activation (Panel A) and deactivation (Panel B) in participants responding to sadness provocation.

Table 3

*Differences in Regional Activation and Deactivation to Sadness Provocation*

| Anatomic Region | BA | Side | Cluster Size | Peak Z | x | y | z (mm) |
|---|---|---|---|---|---|---|---|
| **Activated Regions** | | | | | | | |
| Cuneus/precuneus/posterior-middle cingulate | 7/23/30 | B | 808 | Inf | -6 | -52 | 32 |
| Cerebellum/Vermis | - | B | 972 | Inf | -18 | -76 | -34 |
| Superior medial frontal/superior frontal/ middle frontal/medial orbitofrontal/anterior cingulate | 10/32/ 34/46 | B | 1183 | 7.19 | 6 | 56 | 17 |
| Angular/supramarginal/ middle temporal | 22/39/ 40/41 | L | 318 | 7.16 | -54 | -58 | 32 |
| Angular/supramarginal/ middle-superior temporal | 22/39/ 40/41/ 42/48 | R | 503 | 7.06 | 51 | -52 | 26 |
| Cerebellum | - | R | 107 | 7.03 | 24 | -76 | -31 |
| Thalamus/caudate/putamen/ pallidum/insula/inferior frontal | 25/45/ 47/48 | B | 1649 | 6.80 | 6 | -4 | -1 |
| Middle temporal | 20/21 | L | 59 | 5.30 | -57 | -19 | -16 |
| Middle-inferior temporal | 20 | R | 98 | 5.02 | 51 | -22 | -13 |
| Cerebellum | - | L | 27 | 4.88 | -36 | -58 | -31 |
| Middle-superior frontal | 9 | R | 42 | 4.26 | 21 | 29 | 35 |
| Middle cingulate | 23 | B | 30 | 4.24 | 0 | -13 | 38 |
| Cerebellum | - | R | 21 | 3.85 | 36 | -55 | -31 |
| Middle frontal | 46/48 | L | 27 | 3.56 | -33 | 26 | 32 |

Table 3 (continued)

*Differences in Regional Activation and Deactivation to Sadness Provocation*

| Anatomic Region | BA | Side | Cluster Size | Peak Z | x | y | z (mm) |
|---|---|---|---|---|---|---|---|
| **Deactivated Regions** | | | | | | | |
| Insula/superior temporal/rolandic operculum/postcentral supramarginal/precentral/ inferior frontal/precuneus/ superior-inferior parietal/ middle-superior occipital | 2/3/4/5/ 6/7/18/ 19/20/ 22/37/ 40/41/ 42/43/ 44/48 | B | 6436 | Inf | 54 | -13 | 2 |
| Middle-superior frontal | 6/8 | L | 211 | 6.82 | -24 | 2 | 56 |
| Anterior-middle cingulate | 23/24 | B | 93 | 6.02 | -3 | 5 | 26 |
| Thalamus | 27 | R | 40 | 4.43 | 15 | -25 | 2 |
| Inferior frontal | 45/47/ 48 | L | 71 | 5.09 | -42 | 38 | 5 |
| Middle cingulate | 23 | L | 27 | 4.45 | -12 | -25 | 38 |
| Middle cingulate | - | R | 33 | 4.04 | 15 | -28 | 41 |

*Note.* BA = Brodmann Area, L = left, R = right, B = bilateral, Inf = infinite,

Table 4

*Differences in Regional Activation and Deactivation to Sadness Provocation Across Intervention, Time, Relapse Status*

| Anatomic Region | BA | Side | Cluster Size | Peak Z | x | y | z (mm) |
|---|---|---|---|---|---|---|---|
| **Regions of Interest** | | | | | | | |
| *Non-relapse > Relapse* | | | | | | | |
| Posterior insula | 48 | R | 38 | 3.10 | 39 | -10 | 5 |
| *Pre-treatment > Post-treatment* | | | | | | | |
| Posterior insula | 48 | R | 33 | 3.17 | 45 | -1 | 8 |
| *CBT > MBCT* | | | | | | | |
| Medial prefrontal | 32 | L | 26 | 2.89 | -3 | 41 | 8 |
| *Intervention x Relapse* | | | | | | | |
| Medial prefrontal | 32 | L | 20 | 2.82 | -6 | 44 | 8 |
| **Whole Brain Regions** | | | | | | | |
| *Non-relapse > Relapse* | | | | | | | |
| Inferior frontal/precentral gyrus | 44/48 | L | 25 | 3.90 | -36 | 5 | 23 |
| Superior frontal | 8 | R | 25 | 3.60 | 18 | 8 | 50 |
| Postcentral gyrus | 3 | R | 22 | 3.45 | 36 | -25 | 41 |
| *Intervention x Time* | | | | | | | |
| Putamen | 34/48 | L | 27 | 3.97 | -30 | 2 | -7 |
| Superior frontal/superior medial frontal | 8/32 | L | 20 | 3.53 | -9 | 35 | 41 |
| Middle cingulate | 23 | L | 32 | 3.30 | -15 | -43 | 35 |
| Angular gyrus/middle occipital | 39 | R | 20 | 2.99 | 42 | -58 | 26 |
| *Intervention x Time x Relapse Status* | | | | | | | |
| Superior frontal/medial frontal | 32 | L | 21 | 3.51 | -15 | 35 | 41 |

Table 4 (continued)

*Differences in Regional Activation and Deactivation to Sadness Provocation Across Intervention, Time, Relapse Status*

| Anatomic Region | BA | Side | Cluster Size | Peak Z | x | y | z (mm) |
|---|---|---|---|---|---|---|---|
| *Intervention x Time x Relapse Status* | | | | | | | |
| Superior temporal pole/inferior frontal | 38/45/ 47/48 | L | 31 | 3.47 | -54 | 11 | -1 |
| Middle temporal | 21/22 | L | 31 | 3.36 | -54 | -40 | -1 |
| Posterior cingulate/middle cingulate | 23/26 | L | 20 | 3.33 | -9 | -40 | 26 |

*Note.* BA = Brodmann Area, CBT = Cognitive Behavioral Therapy, L = left, M = Mindfulness-based Co
Therapy, R = right.

### 3.4.1 ROI Analyses

The rPIC and MPFC were analyzed as *a priori* ROIs, and hypothesized to be indicative of relapse prophylaxis and vulnerability, respectively. Differential rPIC activity was captured in contrasts of relapse statuses, with relapsers generally showing greater rPIC deactivation than non-relapsers, $Z = 3.10$, $p = 0.001$ (see Figure 2). No statistically significant interaction effects were found between relapse status and time, intervention, and time by intervention. Significant differential MPFC activity was not captured in contrasts of relapse status or its interactions with time and/or intervention.

### 3.4.2 Whole Brain Analyses

Relative to relapsers, non-relapsers exhibited less deactivation of several cortical regions, including the (1) left rolandic operculum, pars operculum of the inferior frontal cortex, and precentral region (BA 44/48); (2) right middle and superior frontal regions (BA 6/8); (3) right postcentral and supramarginal regions (BA 3/4/40); (4) right superior temporal (BA 1/22); (5) left lingual and cerebellum (BA 18/19); (6) left postcentral and precentral (BA 3/4/6); (7) left postcentral and inferior parietal (BA 4/48); and (8) right insula (BA 48). No interaction effect of relapse status by time was found.

Conjunction analyses comparing relapse status at across time revealed that, of the aforementioned activated clusters, only activity of the (1) left pars operculum of the inferior frontal cortex and precentral region (BA 44/48); (2) right superior frontal regions (BA 8); and (3) right postcentral region (BA 3) were significant at both pre- and post-treatment, suggesting that these functional clusters were pre-existing, intervention-invariant markers of relapse (see Figure 3).

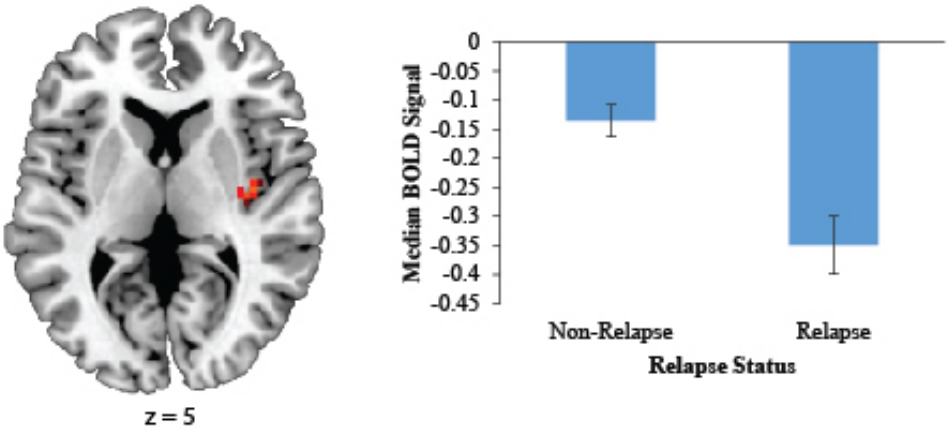


*Figure 2*. Differences in median regional deactivation of the right posterior insula (rPIC) between non-relapsers and relapsers collapsed across intervention and time in response to sadness provocation. Relapsers exhibited greater deactivation of the rPIC relative to non-relapsers.

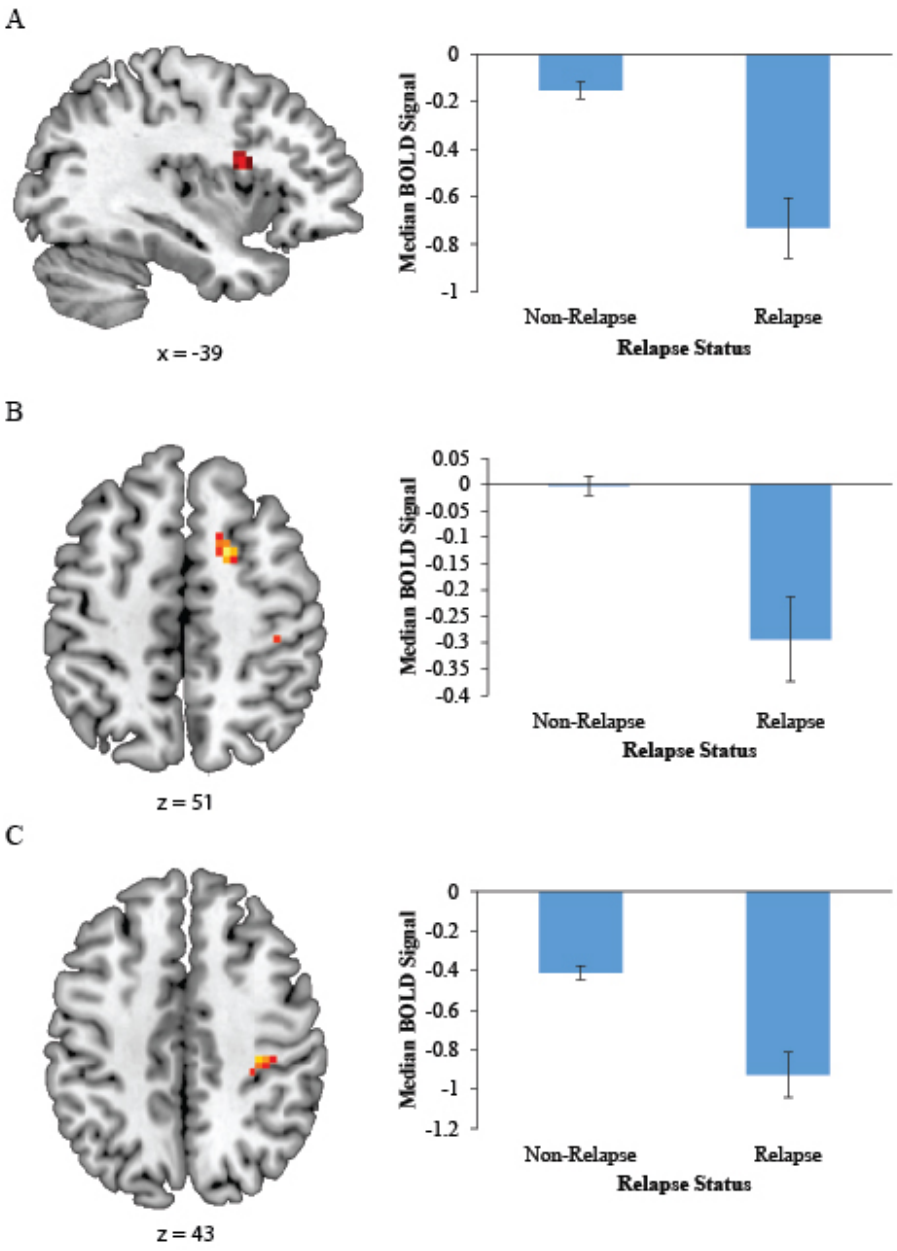


*Figure 3*. Differences in median regional deactivation between non-relapsers and relapsers in the left pars operculum of the inferior, frontal cortex, and precentral region (Panel A), right superior frontal regions (Panel B), and right postcentral region (Panel C). Each functional cluster exhibited similar patterns of activation, with relapsers showing increased deactivation of the foregoing structures relative to non-relapsers.

## 3.5 Effects of Treatment on Neural Reactivity

To ascertain how neural reactivity to sadness challenge varied with intervention group, both (1) the interaction between intervention group and time and (2) group comparisons restricted to the post-treatment were employed (see Table 4 for further details).

### 3.5.1 ROI Analyses

For the rPIC, no main effect of intervention or interactions of intervention by time and/or relapse status were observed, though a main effect of time, $Z = 3.17$, $p < .001$, indicated that the rPIC was deactivated further from pre- to post-treatment (see Figure 4a).

The MPFC was subjected to the same analyses to determine whether differences exist between intervention groups. A main effect of group was observed, such that CBWT participants exhibited greater activation in the left MPFC than MBCT participants, $Z = 2.89$, $p = .002$ (see Figure 4b). An interaction of treatment group and relapse status was also significant, $Z = 2.82$, $p = .002$ (see Figure 4c). MBCT non-relapsers relative to relapsers exhibited greater activation of the MPFC, $Z = 3.30$, $p < .001$, whereas no differences in activity were seen in CBWT relapsers and non-relapsers (see Figure 4). Bar graphs illustrating mean reactivity at each factor level suggest that these interactions may be driven primarily by signal change for CBWT relapsers; however, visual inspection of Figure 4c, which represents the *median* cluster signal value, illustrates a sizeable difference between CBWT relapsers and non-relapsers. Finally, conjunction analyses revealed that the relapse status differences at pre- and post-treatment clusters did not overlap in MBCT.

### 3.5.2 Whole Brain Analyses

Several regions emerged with the time by intervention interaction, including the (1) left putamen (BA 34/48); (2) left superior and superior medial frontal (BA 8/32); (3) left middle

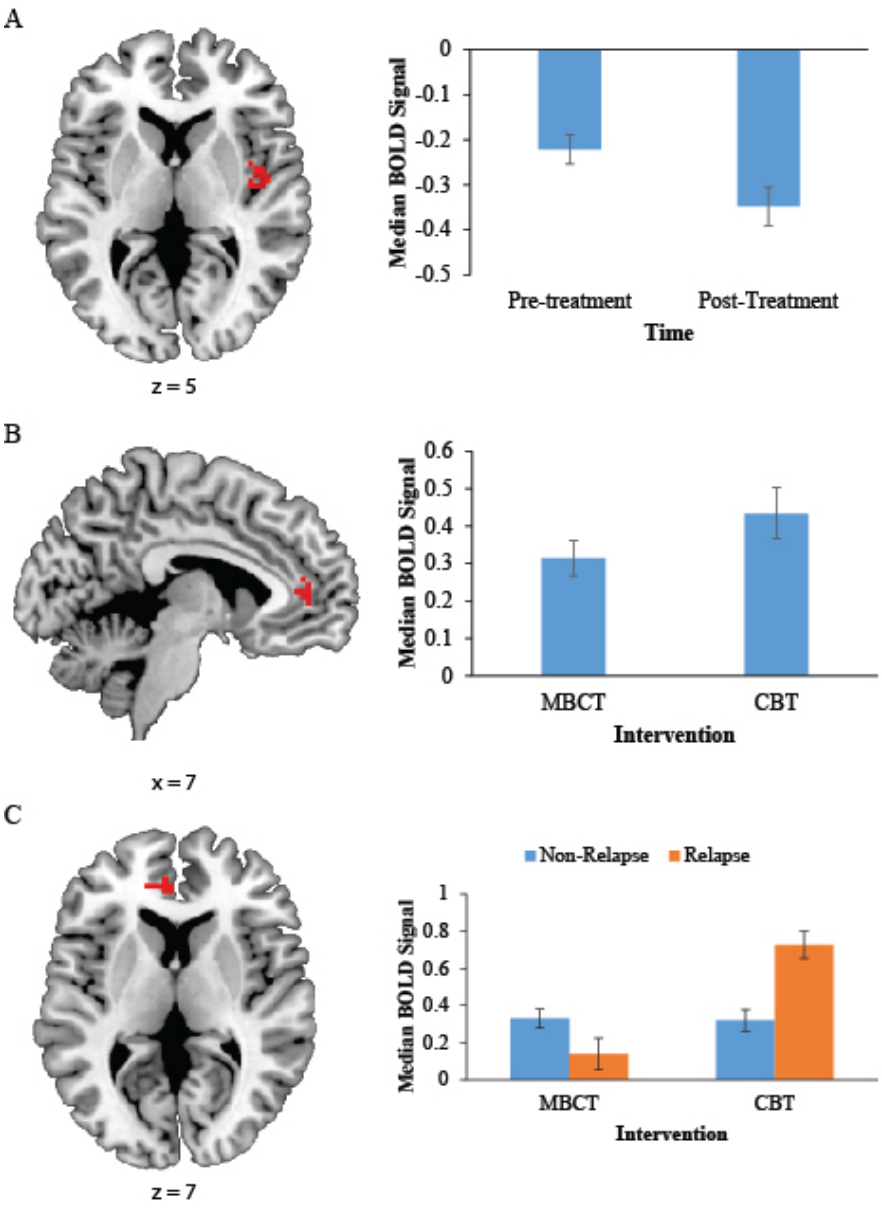


*Figure 4*. Differences in median regional activation in the right posterior insula (rPIC) (Panel A) and medial prefrontal cortex (MPFC) (Panels B and C). Panel A: Participants at post-treatment exhibited greater deactivation of the rPIC than relapsers. Panel B: CBT participants exhibited greater activation of the MPFC relative to MBCT participants. Panel C: MBCT non-relapsers exhibited greater activity of the MPFC relative to MBCT relapsers, though CBT non-relapsers exhibited less activation than CBT relapsers.

cingulate (BA 23); and (4) right angular and middle occipital (BA 39) (see Figures 5 and 6). Contrasts of interventions at each time point and pre-post changes for each intervention were not significant and did not capture these regional clusters. Bar graphs illustrating mean reactivity at each factor level suggest that these interactions may be driven primarily by decreased activation for CBWT participants at post-treatment, though inspection of bar graphs illustrating median reactivity indicates that MBCT may still significantly differ across time, showing greater activation at post-treatment relative to pre-treatment.

A three-way interaction effect among intervention, time, and relapse status was found for the (1) left superior and medial frontal (BA 32); (2) left superior temporal pole and inferior frontal (BA 38/45/47/48); (3) left middle temporal (BA 21/22); and (4) left posterior and middle cingulate (BA 23/26) (see Figures 7, 8, and 9). Post-treatment contrasts of intervention groups by relapse status showed that MBCT differed from CBWT in that MBCT relapsers evinced greater activation of the left middle temporal gyrus (BA 21/22) relative to CBWT relapsers. No differences were detected between MBCT and CBWT non-relapsers.

Comparisons of MBCT and CBWT at pre- and post-treatment revealed that, relative to CBWT, the MBCT group exhibited increased activation of the left middle temporal gyrus (BA 21/22) at post-treatment, while also exhibiting increased activation of several regions at pre-treatment, including the left middle occipital and middle temporal (BA 19/37) and the right inferior and middle temporal (BA 37). Conversely, the CBWT group exhibited greater activity in the right thalamus, right superior temporal (BA 48), and left middle and post cingulate (BA 23/26) relative to the MBCT group at pre-treatment. Conjunction analyses of independent intervention-related changes for the MBCT and CBWT groups were non-significant, indicating a lack of overlap in intervention-related reactivity change between the two groups.

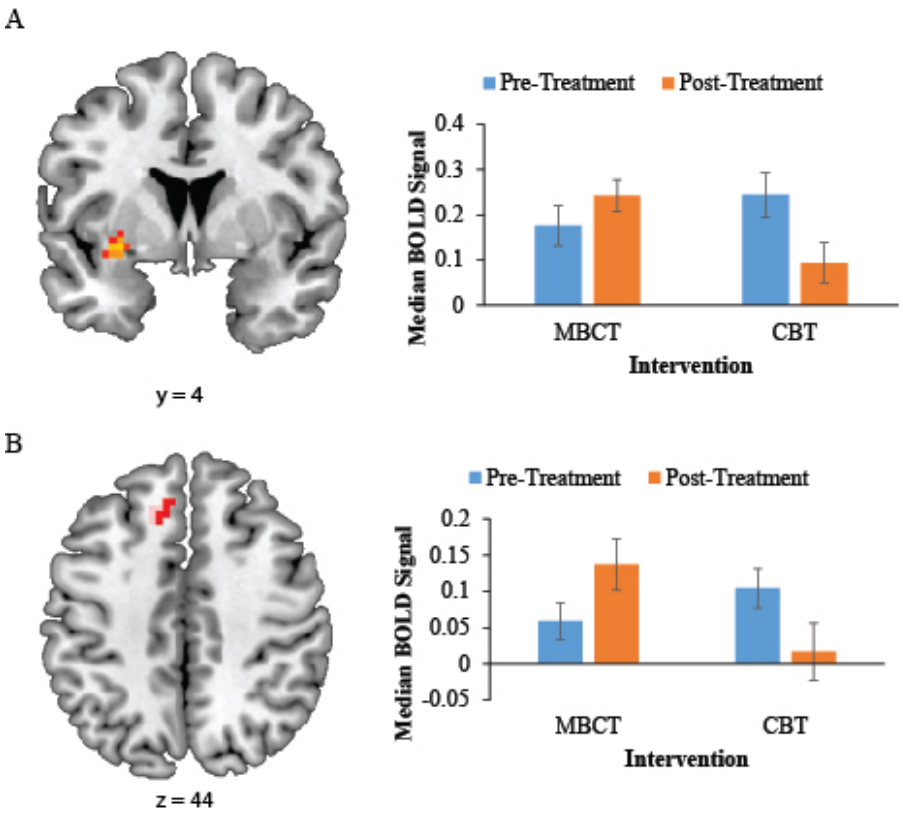


*Figure 5*. Differences in median regional activation of the left putamen (Panel A) and left superior and superior medial frontal (SF/SMF) (Panel B). Panel A: MBCT relapsers appear to have greater activation of the putamen relative to MBCT non-relapsers, whereas CBT relapsers show greater deactivation of the putamen relative to CBT non-relapsers. Panel B: The same pattern of activation is shown here; MBCT relapsers show greater activation of the left SF/SMF relative to MBCT non-relapsers, whereas CBT relapsers show greater deactivation of this region relative to CBT non-relapsers.

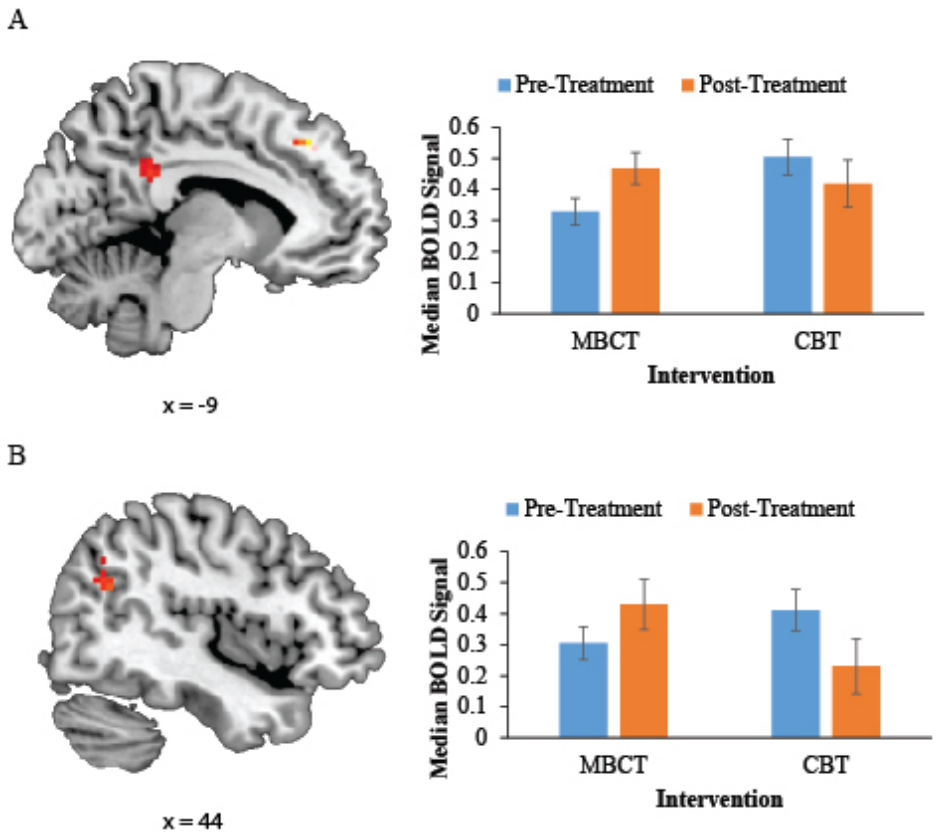


*Figure 6*. Differences in median regional activation of the left middle cingulate (Panel A) and right angular and middle occipital (Panel B). Panel A: MBCT relapsers showed greater activation of the left middle cingulate relative to MBCT non-relapsers, whereas CBT relapsers showed greater deactivation relative to non-relapsers. Panel B: The same pattern of results is shown here; MBCT relapsers show greater activation of the right angular and middle occipital relative to MBCT non-relapsers, whereas CBT relapsers show greater deactivation of this region relative to CBT non-relapsers.

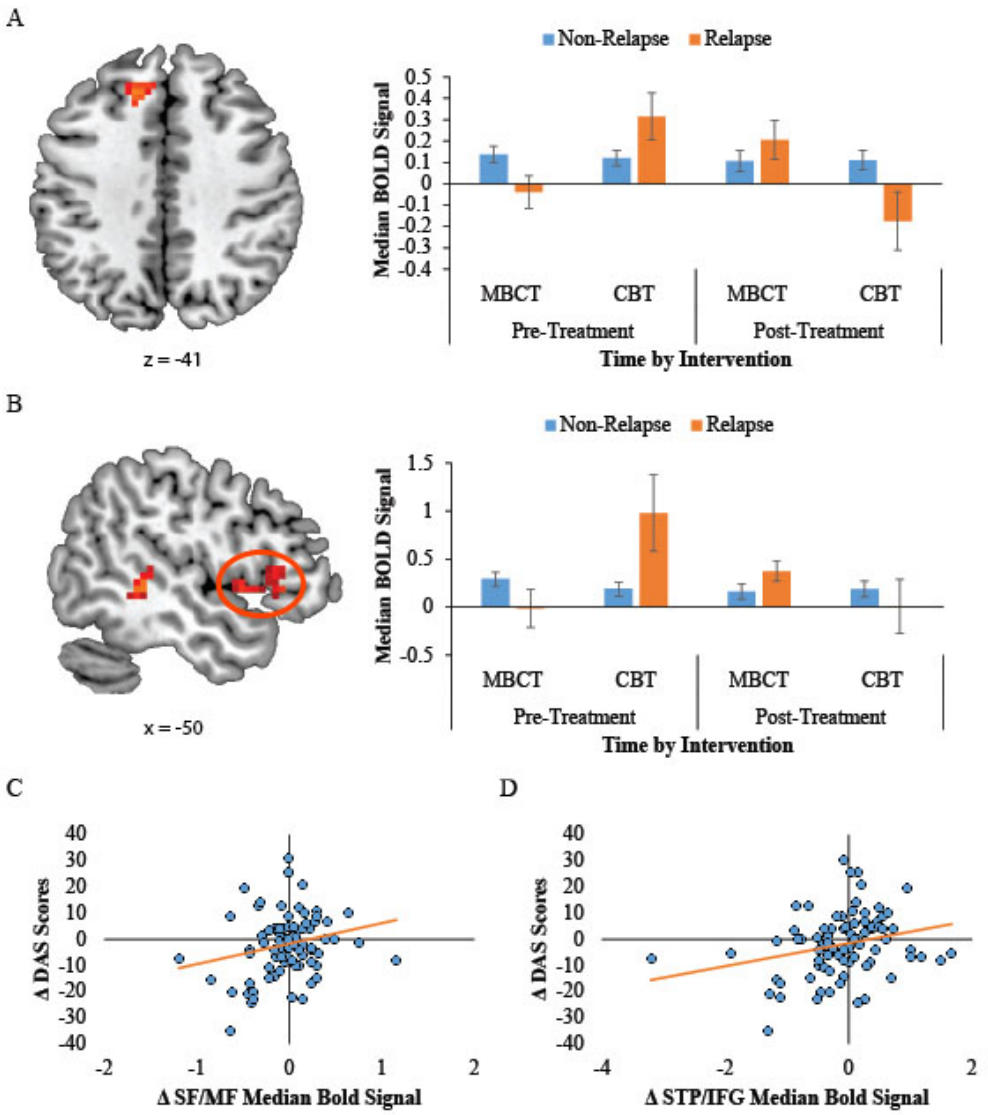


*Figure 7*. Differences in regional activation in the left superior and medial frontal (SF/MF) (Panel A) and left superior temporal pole and inferior frontal (STP/IFG) (Panel B) between relapsers and non-relapsers within the MBCT and CBT interventions across both time points. Panels A and B show the similar a pattern of results, wherein non-relapsers from both groups are relatively stable across time, whereas MBCT and CBT relapsers show increases and decreases in pre-post activation, respectively. Panels C and D: Positive correlations between signal change in the SF/MF (Panel C) and STP/IFG (Panel D), with change in pre-post DAS scores indicating that as brain signals increase across time, self-reported dysfunctional attitudes increase, as well.

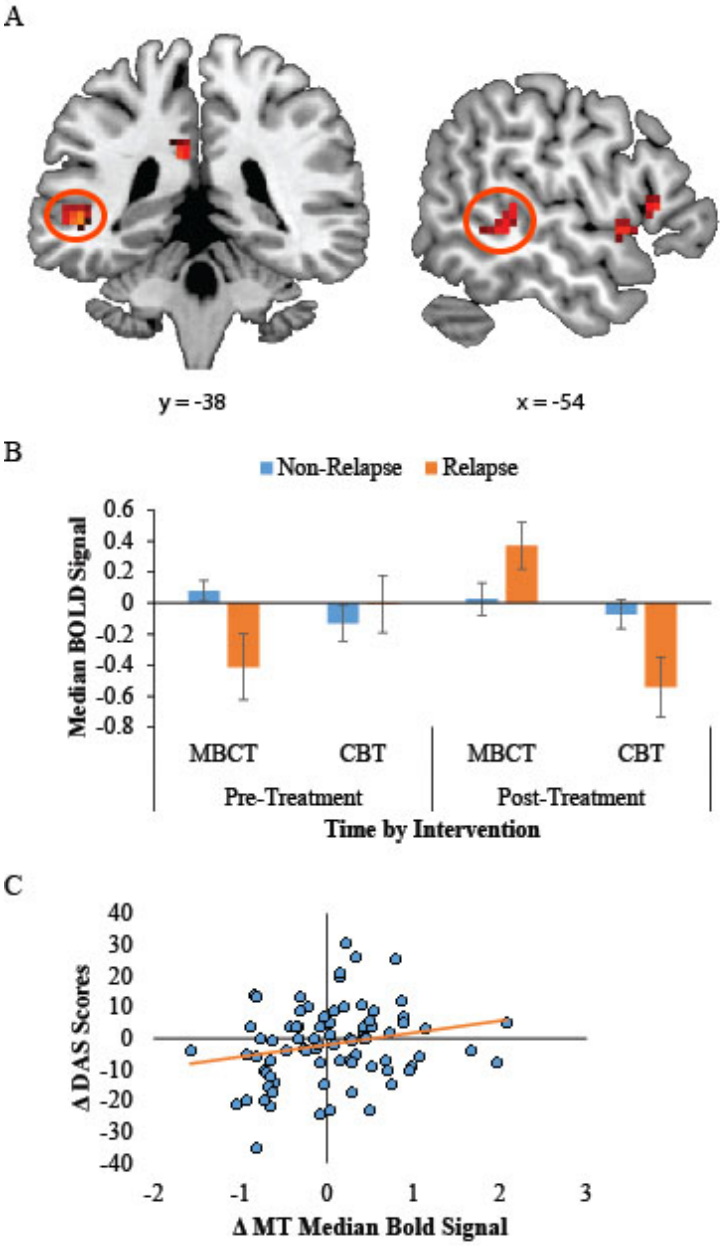


*Figure 8*. Differences in regional activation of the left middle temporal (MT) (Panel A and B), along with correlations between MT signals and DAS scores. Panel A and B: Non-relapsers show relative stability in activation of the MT across time, whereas MBCT and CBT relapsers show increased pre-post activation and deactivation, respectively. Panel C: Positive correlation between pre-post MT activation and DAS scores indicated that MT signals increasing across time corresponded with increases in self-reported dysfunctional attitudes from pre to post.

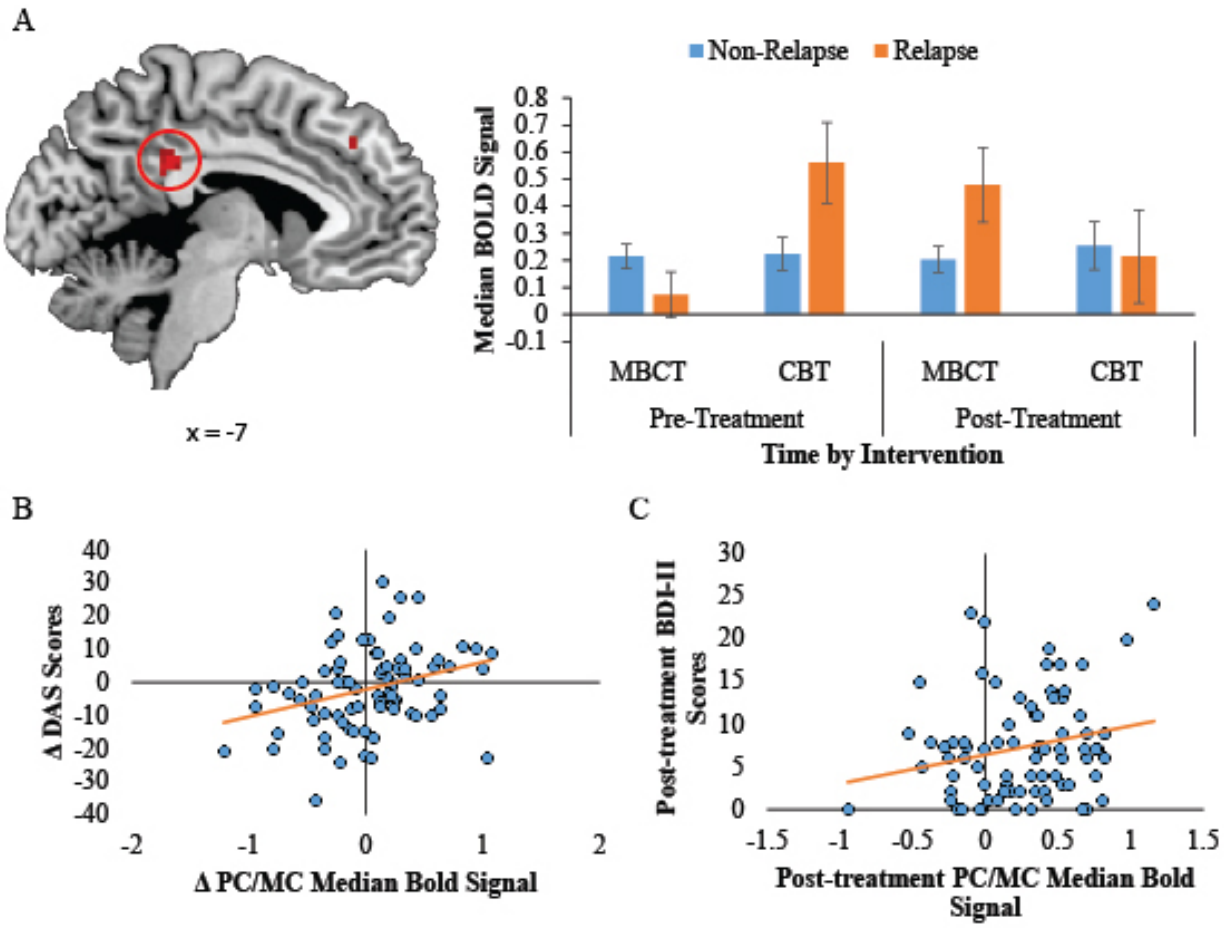


*Figure 9*. Differences in regional activation of the left posterior and middle cingulate (PC/MC) (Panel A), along with correlations PC/MC signals and DAS and BDI-II scores. Panel A: Non-relapsers from both groups show relative stability in PC/MC signals across time, whereas MBCT and CBT relapsers show increased activation and deactivation, respectively. Panels B and C: Positive correlations between change in pre-post PC/MC activation and DAS and BDI-II scores indicated that MT signals increasing across time corresponded with increased self-reported dysfunctional attitudes and depressive symptoms from pre to post.

## 3.6 Associates Among Neural and Behavioral Reactivity and Clinical Symptoms

Exploratory Pearson correlations were run using extracted median signal scores, self-report measures (i.e. BAQ, BDI-II, BAI, DAS, HRSD, and RSQ-R), and sadness reactivity. For measures administered at two time points, change scores were computed by subtracting self-report scores at post-treatment by scores at pre-treatment to ascertain whether changes in brain signals predicted change in clinically relevant constructs.

### 3.6.1 Self-Report Correlations

Relapse status and intervention group were correlated with self-report post-treatment and change scores (see Table 5). Relapse status positively correlated with change in behavioral sadness reactivity across time points, $r = .23$, $p < .05$, wherein relapsers ($M = .18$) exhibited greater reactivity than did non-relapsers ($M = -.43$). Relapse status also positively correlated with post-treatment BAI, $r = .22$, $p < .05$, and HRSD scores, $r = .25$, $p < .05$, in which relapsers exhibited greater anxiety ($M = 10.63$) and depressive symptoms ($M = 3.82$) relative to non-relapsers at post-treatment (BAI: $M = 7.54$; HRSD: $M = 2.02$). Finally, intervention group was associated with HRSD scores at post-treatment, $r = 2.42$, $p < .05$, with the CBWT group reporting higher depressive symptoms at post-treatment ($M = 3.21$) than the MBCT group ($M = 1.78$).

Behavioral sadness reactivity change scores and scores at post-treatment were also correlated with the foregoing self-report measures. Change in sadness reactivity was positively correlated with change in BAI scores, $r = .22$, $p < .05$, indicating that as sadness reactivity increases, reported anxiety increases. In addition, sadness reactivity at post-treatment correlated with BDI-II scores, $r = .23$, $p < .05$, indicating that greater reactivity is associated with greater

Table 5

*Correlations among Intervention, Relapse Status, and Sadness Reactivity with Self-report Post-Treatment and Change Scores*

| | **Intervention** | | **Relapse** | | **Sadness Reactivity** | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | ***Post-treatment*** | | ***Pre-Post*** | |
| | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* |
| **Intervention** | - | - | -.021 | .851 | -.092 | .413 | .000 | .999 |
| **Relapse Status** | -.021 | .851 | - | - | .053 | .636 | .228* | .041 |
| **Pre-Post Change** | | | | | | | | |
| Sadness Reactivity | .000 | .999 | .228* | .041 | .538** | .000 | - | - |
| BAQ | -.070 | .534 | .158 | .160 | -.079 | .484 | .047 | .679 |
| BAI | .034 | .765 | .071 | .530 | .084 | .455 | .220* | .049 |
| BDI-II | .039 | .732 | -.073 | .520 | .019 | .864 | .169 | .131 |
| DAS | -.087 | .439 | .141 | .211 | .158 | .158 | .003 | .978 |
| HRSD | .119 | .289 | .196 | .079 | -.127 | .259 | -.117 | .299 |
| RSQ | -.204 | .068 | -.072 | .524 | -.070 | .536 | .143 | .203 |
| **Post-treatment** | | | | | | | | |
| Sadness Reactivity | -.092 | .413 | .053 | .636 | - | - | .538** | .000 |
| BAQ | -.045 | .691 | .183 | .102 | .032 | .775 | .118 | .293 |
| BAI | .153 | .172 | .220* | .048 | .106 | .345 | .162 | .149 |
| BDI-II | .068 | .544 | .073 | .517 | .230* | .039 | .104 | .354 |
| DAS | .080 | .476 | .075 | .505 | .152 | .176 | .077 | .493 |
| HRSD | .242* | .029 | .251* | .024 | -.087 | .442 | -.111 | .325 |
| RSQ | -.101 | .367 | .124 | .269 | .187 | .095 | .157 | .160 |

*Note.* * $p < .05$, ** $p < .01$. BAI = Beck Anxiety Inventory, BAQ = Body Awareness Questionnaire, BDI-II = Beck Depression Inventory – Version 2, DAS = Dysfunctional Attitude Scale, HRSD = Hamilton Rating Scale for Depression, IxT = Intervention by Time interaction, mPFC = medial prefrontal cortex, *r* = Pearson correlation, RSQ = Response Style Questionnaire.

self-reported depressive symptoms.

### 3.6.2 ROI Analyses

The conjunction between the relapse status and time contrasts showed an overlap only in miniscule separate, nearby clusters of the right PIC, $Z = 2.15$, $k = 9$, $p < .05$, suggesting that, although there are shared clusters, these contrasts target largely separate portions of the right PIC (see Figure 10). Nevertheless, only the extracted signals from the shared MPFC and right PIC cluster were included in exploratory correlational analyses (see Table 6).

Activity within the right PIC cluster at post-treatment negatively correlated with relapse status, $r = -.261$, $p < .05$, indicating that relapsers relative to non-relapsers showed less activation of the rPIC following therapy. No other intervention or relapse status differences were detected.

No significant correlations were detected between the right PIC and any self-report measures. In contrast, pre-post change in left MPFC activation correlated positively with pre-post sadness reactivity scores, $r < .220$, $p < .05$, indicating that increases in MPFC across time coincided with increases in sadness reactivity across time. Pre-post change in the MPFC also correlated with post-treatment BAI, $r < .315$, $p < .005$, and BDI-II scores, $r < .256$, $p < .05$, wherein a rise in MPFC activity across time corresponds to greater self-reported anxiety and depressive symptoms at post-treatment. Finally, MPFC activity at post-treatment correlated with DAS scores at post-treatment, $r < -.224$, $p < .05$, indicating that increases in MPFC activity corresponds with increases in endorsed dysfunctional attitudes.

### 3.6.3 Whole Brain Analyses

Correlational findings between pre-post and post-treatment neural activity and self-report scores are reported in Tables 7 to 12.

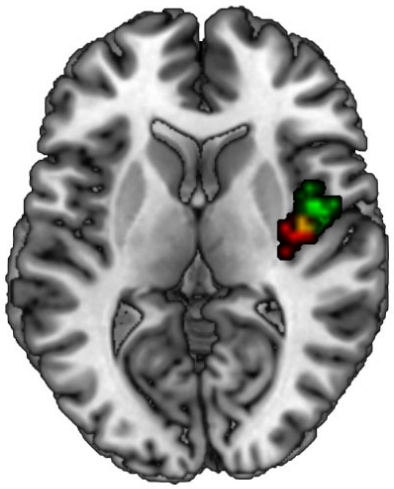

*Figure 10*. Differences in rPIC activation emerging from relapse status and time differences. The green portion reflects rPIC activation emerging from the time contrast (i.e. time 1 – time 2), the red portion reflects rPIC activation emerging from the relapse status contrast (i.e. non-relapse – relapse), and the yellow portion represents the overlap between the two clusters.

Table 6

*Correlations between Regions of Interest and Self-report Post-treatment and Change Scores*

| | rPIC (CNJ) | | | | mPFC (IxT) | | | |
|---|---|---|---|---|---|---|---|---|
| | ***Pre-Post*** | | ***Post-Treatment*** | | ***Pre-Post*** | | ***Post-Treatment*** | |
| | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* |
| **Intervention** | -.004 | .970 | -.108 | .336 | -.014 | .900 | .103 | .362 |
| **Relapse Status** | -.066 | .560 | -.261* | .019 | .065 | .562 | .077 | .495 |
| **Pre-Post Change** | | | | | | | | |
| Sadness Reactivity | .056 | .619 | -.043 | .704 | .214 | .055 | -.136 | .227 |
| BAQ | .027 | .814 | .030 | .788 | .057 | .614 | .096 | .394 |
| BAI | -.178 | .112 | -.190 | .089 | .194 | .083 | .085 | .450 |
| BDI-II | -.070 | .537 | -.052 | .645 | .204 | .068 | .171 | .128 |
| DAS | .103 | .361 | .107 | .341 | .202 | .070 | -.005 | .961 |
| HRSD | -.171 | .127 | -.190 | .089 | -.187 | .095 | .074 | .509 |
| RSQ | -.022 | .843 | .127 | .259 | -.181 | .106 | -.298* | .007 |
| **Post-treatment** | | | | | | | | |
| Sadness Reactivity | -.112 | .319 | -.105 | .349 | .209 | .061 | -.032 | .779 |
| BAQ | -.121 | .284 | -.199 | .075 | .086 | .445 | -.030 | .791 |
| BAI | -.062 | .584 | -.172 | .124 | .308** | .005 | .113 | .317 |
| BDI-II | -.012 | .918 | -.108 | .336 | .244* | .028 | .177 | .113 |
| DAS | -.016 | .886 | -.064 | .569 | -.086 | .443 | -.222* | .047 |
| HRSD | -.059 | .603 | -.170 | .129 | .004 | .971 | .159 | .155 |
| RSQ | -.041 | .717 | -.175 | .118 | .111 | .324 | -.109 | .332 |

*Note.* * $p < .05$, ** $p < .01$. BAI = Beck Anxiety Inventory, BAQ = Body Awareness Questionnaire, BDI-II = Beck Depression Inventory – Version 2, CNJ = Conjunction, DAS = Dysfunctional Attitude Scale, HRSD = Hamilton Rating Scale for Depression, IxT = Intervention by Time interaction, mPFC = medial prefrontal cortex, *r* = Pearson correlation, rPIC = right posterior insular cortex, RSQ = Response Style Questionnaire.

Table 7

*Correlations between Change in Relapse-Related Brain Signals and Self-report Post-treatment and Change Scores*

| | **Left Inferior Frontal/Precentral** | | **Right Superior Frontal** | | **Right Postcentral** | |
|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* |
| **Intervention** | .023 | .841 | -.129 | .251 | .039 | .732 |
| **Relapse Status** | -.405 | .000 | -.397** | .000 | -.413** | .000 |
| **Pre-Post Change** | | | | | | |
| Sadness Reactivity | -.045 | .687 | -.054 | .632 | -.174 | .121 |
| BAQ | -.056 | .622 | .039 | .730 | -.158 | .134 |
| BAI | .004 | .972 | -.113 | .317 | -.097 | .389 |
| BDI-II | .069 | .541 | .130 | .249 | -.021 | .853 |
| DAS | .066 | .561 | -.060 | .586 | .119 | .291 |
| HRSD | -.069 | .541 | -.117 | .300 | -.145 | .197 |
| RSQ | -.022 | .844 | .032 | .777 | -.036 | .749 |
| **Post-treatment** | | | | | | |
| Sadness Reactivity | -.171 | .127 | -.237* | .033 | -.106 | .346 |
| BAQ | -.312** | .005 | -.103 | .359 | -.210 | .060 |
| BAI | -.024 | .828 | .007 | .953 | -.016 | .884 |
| BDI-II | .095 | .399 | -.074 | .513 | -.031 | .782 |
| DAS | .047 | .680 | -.041 | .715 | .008 | .946 |
| HRSD | -.028 | .803 | -.213 | .056 | -.059 | .601 |
| RSQ | .034 | .762 | -.103 | .360 | -.049 | .667 |

*Note.* * $p < .05$, ** $p < .01$. BAI = Beck Anxiety Inventory, BAQ = Body Awareness Questionnaire, BDI-II = Beck Depression Inventory – Version 2, DAS = Dysfunctional Attitude Scale, HRSD = Hamilton Rating Scale for Depression, *r* = Pearson correlation, RSQ = Response Style Questionnaire.

Table 8

*Correlations between Post-treatment Relapse-Related Brain Signals and Self-report Post-treatment and Change Scores*

| | **Left Inferior Frontal/Precentral** | | **Right Superior Frontal** | | **Right Postcentral** | |
|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* |
| **Intervention** | .048 | .673 | .032 | .778 | .155 | .167 |
| **Relapse Status** | -.009 | .939 | -.015 | .896 | -.046 | .682 |
| **Pre-Post Change** | | | | | | |
| Sadness Reactivity | .046 | .681 | -.012 | .915 | -.098 | .383 |
| BAQ | .134 | .232 | .074 | .509 | -.003 | .979 |
| BAI | .131 | .243 | .059 | .601 | -.124 | .270 |
| BDI-II | .147 | .190 | .194 | .083 | -.075 | .505 |
| DAS | .158 | .158 | -.099 | .379 | .093 | .407 |
| HRSD | -039 | .727 | .147 | .191 | -.044 | .699 |
| RSQ | -.076 | .499 | .022 | .842 | .004 | .968 |
| **Post-treatment** | | | | | | |
| Sadness Reactivity | -.241* | .030 | -.292** | .008 | -.181 | .106 |
| BAQ | -.188 | .093 | .015 | .895 | -.176 | .116 |
| BAI | .049 | .663 | .124 | .269 | -.043 | .702 |
| BDI-II | .223* | .046 | .064 | .568 | -.036 | .751 |
| DAS | .128 | .253 | .071 | .532 | .100 | .373 |
| HRSD | .130 | .247 | .173 | .123 | .080 | .478 |
| RSQ | -.053 | .639 | -.017 | .878 | -.052 | .646 |

*Note.* * $p < .05$, ** $p < .01$. BAI = Beck Anxiety Inventory, BAQ = Body Awareness Questionnaire, BDI-II = Beck Depression Inventory – Version 2, DAS = Dysfunctional Attitude Scale, HRSD = Hamilton Rating Scale for Depression, *r* = Pearson correlation, RSQ = Response Style Questionnaire.

Table 9

*Correlations between Post-treatment Brain Signals from the Intervention by Time Contrast and Self-report Scores*

| | **Putamen** | | **Superior/Superior Medial Frontal** | | **Middle Cingulate** | | **Angular Gyrus/ Middle Occipital** | |
|---|---|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* |
| **Intervention** | -.126 | .263 | -.059 | .599 | -.227* | .041 | -.022 | .845 |
| **Relapse Status** | -.084 | .457 | .042 | .711 | .008 | .942 | .150 | .180 |
| **Pre-Post Change** | | | | | | | | |
| Sadness Reactivity | .059 | .602 | -.015 | .892 | -.062 | .583 | .061 | .591 |
| BAQ | -.023 | .838 | -.118 | .295 | .032 | .780 | .191 | .088 |
| BAI | -.055 | .628 | .071 | .531 | .045 | .691 | .066 | .560 |
| BDI-2 | .014 | .903 | -.102 | .367 | -.110 | .329 | .063 | .575 |
| DAS-17 | .114 | .311 | .336** | .002 | .220* | .049 | .173 | .123 |
| HRSD-17 | -.070 | .536 | -.074 | .513 | -.070 | .533 | -.068 | .549 |
| RSQ-25 | -.174 | .121 | -.105 | .349 | -.046 | .682 | -.115 | .306 |
| **Post-treatment** | | | | | | | | |
| Sadness Reactivity | .023 | .841 | -.058 | .609 | .027 | .809 | .148 | .186 |
| BAQ | -.087 | .440 | -.272* | .014 | -.103 | .358 | .013 | .905 |
| BAI | .101 | .372 | .031 | .781 | .027 | .809 | .211 | .058 |
| BDI-2 | -.022 | .847 | -.054 | .632 | .006 | .954 | .224* | .045 |
| DAS-17 | -.013 | .911 | .028 | .803 | -.002 | .983 | .199 | .074 |
| HRSD-17 | -.129 | .249 | .013 | .908 | -.047 | .678 | .011 | .919 |
| RSQ-25 | -.122 | .277 | -.187 | .094 | -.012 | .916 | .129 | .250 |

*Note.* * $p < .05$, ** $p < .01$. BAI = Beck Anxiety Inventory, BAQ = Body Awareness Questionnaire, BDI-II = Beck Depression Inventory – Version 2, DAS = Dysfunctional Attitude Scale, HRSD = Hamilton Rating Scale for Depression, *r* = Pearson correlation, RSQ = Response Style Questionnaire.

Table 10

*Correlations between Change in Brain Signals from the Intervention by Time Contrast and Self-report Scores*

| | **Putamen** | | **Superior/Superior Medial Frontal** | | **Middle Cingulate** | | **Angular Gyrus/ Middle Occipital** | |
|---|---|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* |
| **Intervention** | -.193 | .084 | -.123 | .272 | -.136 | .225 | -.134 | .234 |
| **Relapse Status** | -.044 | .696 | -.057 | .614 | .145 | .197 | .079 | .484 |
| **Pre-Post Change** | | | | | | | | |
| Sadness Reactivity | .210 | .060 | .094 | .402 | .100 | .377 | .183 | .101 |
| BAQ | -.054 | .633 | -.061 | .587 | .011 | .919 | .033 | .769 |
| BAI | .057 | .612 | .105 | .352 | .065 | .565 | .145 | .196 |
| BDI-2 | -.038 | .738 | -.047 | .680 | -.149 | .184 | .101 | .372 |
| DAS-17 | .220* | .048 | .260* | .019 | .219* | .049 | .318** | .004 |
| HRSD-17 | -.169 | .132 | -.251* | .024 | -.190 | .090 | -.212 | .058 |
| RSQ-25 | -.105 | .350 | -.136 | .225 | -.048 | .668 | -.080 | .479 |
| **Post-treatment** | | | | | | | | |
| Sadness Reactivity | .103 | .360 | .064 | .568 | .050 | .660 | .156 | .165 |
| BAQ | -.004 | .974 | -.092 | .414 | -.201 | .073 | -.057 | .014 |
| BAI | .223* | .045 | .201 | .072 | .072 | .526 | .316** | .004 |
| BDI-2 | -.008 | .946 | .124 | .270 | .023 | .839 | .273* | .014 |
| DAS-17 | .024 | .830 | .039 | .732 | -.062 | .582 | .156 | .163 |
| HRSD-17 | -.116 | .301 | -.068 | .545 | -.076 | .640 | .242* | .029 |
| RSQ-25 | -.042 | .707 | -.060 | .594 | -.051 | .654 | .186 | .097 |

*Note.* * $p < .05$, ** $p < .01$. BAI = Beck Anxiety Inventory, BAQ = Body Awareness Questionnaire, BDI-II = Beck Depression Inventory – Version 2, DAS = Dysfunctional Attitude Scale, HRSD = Hamilton Rating Scale for Depression, *r* = Pearson correlation, RSQ = Response Style Questionnaire.

Table 11

*Correlations between Post-treatment Brain Signals from the Intervention by Time by Relapse Status Contrast and Self-report Scores*

| | **Superior/Medial Frontal** | | **Superior Temporal Pole/Inferior Frontal** | | **Middle Temporal** | | **Posterior/Middle Cingulate** | |
|---|---|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* |
| **Intervention** | *-.257** | *.021* | *-.238** | *.032* | *-.059* | *.600* | *-.184* | *.101* |
| **Relapse Status** | *.013* | *.909* | *-.150* | *.180* | *.114* | *.310* | *-.022* | *.843* |
| **Pre-Post Change** | | | | | | | | |
| Sadness Reactivity | .151 | .178 | -.028 | .802 | -.001 | .993 | .167 | .136 |
| BAQ | .118 | .292 | -.086 | .447 | .120 | .285 | -.174 | .119 |
| BAI | .181 | .106 | -.103 | .361 | .103 | .359 | -.035 | .754 |
| BDI-2 | .160 | .152 | -.020 | .857 | .102 | .363 | -.078 | .490 |
| DAS-17 | .142 | .207 | .086 | .445 | .163 | .147 | .060 | .595 |
| HRSD-17 | -.113 | .315 | -.183 | .102 | -.020 | .862 | -.223* | .045 |
| RSQ-25 | -.109 | .333 | -.226* | .042 | -.109 | .333 | -.263* | .018 |
| **Post-treatment** | | | | | | | | |
| Sadness Reactivity | .106 | .345 | -.008 | .940 | .210 | .059 | .062 | .584 |
| BAQ | -.136 | .227 | -.101 | .371 | -.092 | .416 | -.176 | .117 |
| BAI | .111 | .323 | .055 | .629 | .218 | .051 | -.025 | .824 |
| BDI-2 | .109 | .335 | .009 | .933 | .261* | .019 | -.130 | .249 |
| DAS-17 | -.015 | .895 | -.056 | .623 | .112 | .318 | -.190 | .089 |
| HRSD-17 | -.163 | .145 | -.190 | .090 | .040 | .725 | -.219* | .050 |
| RSQ-25 | -.100 | .375 | -.227* | .042 | .123 | .273 | -.150 | .181 |

*Note.* * $p < .05$, ** $p < .01$. BAI = Beck Anxiety Inventory, BAQ = Body Awareness Questionnaire, BDI-II = Beck Depression Inventory – Version 2, DAS = Dysfunctional Attitude Scale, HRSD = Hamilton Rating Scale for Depression, *r* = Pearson correlation, RSQ = Response Style Questionnaire.

Table 12

*Correlations between Change in Brain Signals from the Intervention by Time by Relapse Status Contrast and Self-report Scores*

| | **Superior/Medial Frontal** | | **Superior Temporal Pole/Inferior Frontal** | | **Middle Temporal** | | **Posterior/Middle Cingulate** | |
|---|---|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* |
| **Intervention** | -.265* | .017 | -.288** | .009 | -.217 | .051 | -.257* | .021 |
| **Relapse Status** | .019 | .864 | -.128 | .256 | .044 | .697 | -.002 | .984 |
| **Pre-Post Change** | | | | | | | | |
| Sadness Reactivity | .283* | .010 | .021 | .853 | .152 | .177 | .298** | .007 |
| BAQ | .131 | .244 | -.130 | .246 | -.040 | .721 | -.163 | .146 |
| BAI | .257* | .021 | -.040 | .723 | .170 | .129 | -.042 | .713 |
| BDI-2 | .131 | .245 | -.105 | .352 | .090 | .425 | -.053 | .641 |
| DAS-17 | .202 | .070 | .216 | .052 | .327** | .003 | .120 | .284 |
| HRSD-17 | -.273* | .014 | -.209 | .061 | -.211 | .058 | -.342** | .002 |
| RSQ-25 | -.085 | .453 | -.207 | .063 | -.055 | .628 | -.217 | .051 |
| **Post-treatment** | | | | | | | | |
| Sadness Reactivity | .166 | .138 | .035 | .758 | .238* | .032 | .201 | .072 |
| BAQ | .072 | .524 | -.035 | .753 | -.111 | .322 | .021 | .854 |
| BAI | .268* | .016 | .125 | .267 | .287** | .009 | .134 | .234 |
| BDI-2 | .160 | .153 | -.017 | .881 | .257* | .021 | .024 | .828 |
| DAS-17 | .134 | .235 | .002 | .984 | .068 | .546 | -.007 | .954 |
| HRSD-17 | -.205 | .067 | -.163 | .146 | -.052 | .644 | -.251* | .024 |
| RSQ-25 | .085 | .448 | -.102 | .367 | .213 | .057 | .015 | .898 |

*Note.* * $p < .05$, ** $p < .01$. BAI = Beck Anxiety Inventory, BAQ = Body Awareness Questionnaire, BDI-II = Beck Depression Inventory – Version 2, DAS = Dysfunctional Attitude Scale, HRSD = Hamilton Rating Scale for Depression, *r* = Pearson correlation, RSQ = Response Style Questionnaire.

Pre-post signals extracted from the clusters emerging as significant in the relapse status contrast did not correlate with any self-report change scores. However, sadness reactivity at post-treatment was associated with pre-post changes in the inferior frontal and precentral cluster, $r$ = -.241, $p$ < .05, and the right superior frontal cluster, $r$ = -.292, $p$ < .01, indicating that increased activation of these clusters across time corresponded with less reactivity to sadness provocation at post-treatment. The left inferior frontal-precentral region also correlated with BDI-II scores at post-treatment, $r$ = .223, $p$ < .05, indicating that greater activity at post-treatment predicted more severe self-reported depressive symptoms. Post-treatment signals from the left inferior frontal and precentral region was associated with post-treatment BAQ scores, $r$ = -.312, $p$ < .01, indicating that greater activation of this region predicted less body awareness. Finally, the right superior frontal cluster was correlated with post-treatment reactivity scores, $r$ = -.237, $p$ < .05, indicating that greater activation of this region corresponded with less sadness reactivity. Change in brain activity did not significantly correlate with either group or relapse, though post-treatment activity was significantly related to relapse status, $p$ < .001, showing that non-relapsers evinced greater activation of these regions relative to non-relapsers (see Tables 7 and 8 for further information).

Signals extracted from the intervention by time interaction, which generally demonstrated less activation in CBWT participants and greater activation in MBCT participants at post-treatment relative to pre-treatment, correlated with a number of pre-post change and post-treatment scores (see Tables 9 and 10). A more notable finding was that the left middle cingulate was correlated with change in DAS scores from pre to post, $r$ = .327, $p$ < .01, indicating that as activation of the middle cingulate increased, so too did dysfunctional attitudes. This cluster also correlated with post-treatment sadness reactivity, $r$ = .238, $p$ < .05, and BDI-II scores, $r$ = .257, $p$ < .05, indicating that increased activity corresponded with increased sadness reactivity and self-

reported depressive symptoms at post-treatment. Furthermore, left middle cingulate at post-treatment was also correlated with BDI-II scores at post-treatment, $r = .261$, $p < .05$, indicating that greater activity corresponded with more severe depressive symptoms at post-treatment. Finally, pre-post change in the right angular and middle occipital correlated with change in sadness reactivity, $r = .298$, $p < .01$, indicating that as activity increased, sadness reactivity also increased. This cluster further correlated with HRSD change scores, $r = -.342$, $p < .01$, and post-treatment scores, $r = -.251$, $p < .05$, showing that increased activity predicted lest depressive symptoms.

Signals extracted from the three-way interaction also correlated with a number of pre-post change scores (see Tables 11 and 12 and Figures 7, 8, and 9). The most notable finding was that DAS-17 change scores correlated with the left superior and medial frontal, $r = .220$, $p < .05$, superior temporal pole and inferior frontal, $r = .260$, $p < .05$, middle temporal, $r = .219$, $p < .05$, and posterior and middle cingulate, $r = .318$, $p < .01$, indicating that as activity in these clusters increased across time, so too did self-reported dysfunctional attitudes. Activity within the left posterior and middle cingulate positively also correlated with post-treatment BAI, r = .316, .005, and BDI-II scores, $r = .273$, $p < .05$, indicating that increases in activity corresponded with higher self-reported anxiety and depressive symptoms following therapy. Finally, post-treatment signals form this same cluster was associated with BDI-II scores at post-treatment, $r = .224$, $p < .05$, showing that increased activity predicted higher self-reported depressive symptoms following therapy.

# 4 Discussion

Findings from the current study contradicted most of the set hypotheses. First, it was predicted that, relative to non-relapsers, relapsers would show greater activation of the MPFC;

however, MPFC activity was not found to be distinguishable as a function of relapse status. Second, the MBCT group was expected to evince increased pre-post activation of the rPIC, though no such increase was observed. Third, the MBCT group was expected to evince decreased pre-post activation of the MPFC, but our findings indicated that only relapsers evinced change in activation, and that this change was reflected as increased *deactivation* of the MPFC. Finally, it was predicted that, relative to the CBWT group, the MBCT group would show greater activation and deactivation of the rPIC and MPFC, respectively. Though the CBT group exhibited more MPFC activation than the MBCT group, no differentiation in rPIC activity was found. Additional analyses indicated that rPIC activity only changed as function of time and relapses status, with post-treatment participants and relapsers showing greater deactivation of the rPIC relative to pre-treatment participants and non-relapsers, respectively. These findings are surprising in that they are largely inconsistent with the two-factor model of vulnerability to depression and the current understanding of the neural mechanisms underlying MBCT.

## 4.1 Behavioral Markers of Relapse and Intervention

Behaviorally, relapsers showed greater change in sadness reactivity to dysphoric cues from pre- to post-treatment than did non-relapsers, implying that relapsers had become more sensitized to sadness provocation regardless of treatment. Furthermore, relapsers exhibited greater anxiety and depressive symptoms than non-relapsers at post-treatment, while the CBWT group reported greater depressive symptoms than the MBCT group at post-treatment. Finally, change in reactivity predicted increased anxiety across time, while post-treatment reactivity predicted greater post-intervention depressive symptoms. Interestingly, however, most of the self-reported anxiety and depressive symptoms at post-treatment fell into the minimal to mild range of severity, thus forcing us to question the meaningfulness of these predictive relationships between sadness reactivity and indices of psychopathology. It is possible that these seemingly

minor differences following therapy constitute the starting point of what becomes a diverging trajectory from normalcy, which eventually results in the reemergence of more severe depressive symptoms. According to descriptions of the 'rollback phenomenon' (Fava, 1999; Fava & Kellner, 1991), these residual and remitting symptoms simultaneously become prodromal symptoms of depression, and if not properly managed, may hasten one's backslide into the old dysphoric fixation-rumination cycle and leave the individual susceptible to full-on major depression.

## 4.2 Neural Markers of Relapse and Intervention

### 4.2.1 Medial Prefrontal Cortex

The MPFC has previously been predictive of rumination in response to sadness provocation and relapse status over an 18-month period (Farb, Anderson, Bloch, & Segal, 2011), but the context of the current study, MPFC activation across time was not associated with rumination and was not predictive of relapse. Nevertheless, change in MPFC activity did correspond with increased sadness reactivity from pre- to post-treatment, and was associated to greater anxiety and depressive symptoms at post-treatment, indicating that it still retained some negative influence over mood. According to Farb, Anderson, Bloch, and Segal (2011), MPFC reactivity during sadness provocation may reflect unsuccessful attempts at regulating evoked negative emotions, which could explain the greater activation seen in CBWT non-relapsers. The MPFC has been implicated in the cognitive reappraisal of negative environmental stimuli (Etkin, Egner, & Kalisch, 2011; Ochsner, Bunge, Gross, & Gabrieli, 2002), and as individuals vulnerable to depression recruit more prefrontal regions to down-regulate negative emotions (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007), it stands to reason that the CBWT relapsers may require more effort to employ cognitive reappraisal successfully in response to

stressors, resulting in greater activation of the MPFC.

In contrast, the lower activation of the MPFC in the MBCT group relative to the CBT group could have resulted from its emphasis on mindfulness skills instead of reappraisal techniques. Whereas MBCT non-relapsers might have been successfully applying their skills in bringing acceptance to dysphoric cues, MBCT relapsers may have been using mindfulness in a maladaptive fashion to alleviate dysfunctional thoughts. For instance, MBCT participants exhibited activation of the left middle temporal where CBT participants saw deactivation, and MBCT relapsers exhibited increased activation of the precentral region following treatment. The left middle temporal and precentral regions have been implicated in reappraisal and distraction, respectively (McRae, et al., 2010), and perhaps co-activations of such structures in relapsers represent the misapplication of emotion regulatory strategies in response to stressors. Distraction is not necessarily a maladaptive self-regulatory strategy; in fact, it is the preferred strategy when managing highly demanding stressors (Sheppes, et al., 2012). However, if applied indiscriminately, it may cost individuals the needed opportunity to fully process emotional events in a way that promotes long-term wellbeing (Sheppes, et al., 2012). Whatever the explanation, both CBWT and MBCT non-relapsers in the current study exhibited comparable MPFC activations, and as Opialla and colleagues (2015) reported that both mindfulness-based and cognitive reappraisal strategies activated the MPFC during down-regulation of negative emotions, it appears that driving neural activation of this midline structure away in either direction from activation levels seen in non-relapsers is maladaptive.

### 4.2.2 Right Posterior Insular Cortex

Considering the purported importance of the right posterior insula in mindfulness-based interventions and skills (Farb, Anderson, Irving, & Segal, 2015), it is surprising that it was more engaged in relapsers and the CBWT group than in non-relapsers and the MBCT group,

respectively. In addition, activity within this structure was not associated with interoceptive awareness, nor was it associated with any measures of depressive symptoms. Although this finding is in stark contrast to a previous study of mindfulness-based interventions and sadness provocation (Farb, et al., 2010), results may have differed for several reasons. Menon and Uddin (2010) postulated that the posterior insula is responsible for integrating motivationally salient sensory attributes, and as there was a decrease in right PIC activation across time, perhaps following psychological treatment, dysphoric cues that are without personal relevance (i.e. movie clips) no longer evoke the same degree of reactivity as they once did. Second, it is possible that the MBCT group exhibited differential engagement of the right PIC in functional connectivity, which may not have been detected by simple contrasts. For instance, in addition to observing increased PIC activity during an interoceptive attention task, Farb, Segal, and Anderson (2013) also reported that mindfulness training promoted negative functional connectivity between the right PIC and DMPFC. Within the current study, differential functional connections between the right PIC and other structures, such as the MPFC, could have distinguished interventions and relapse groups, and as such, will be evaluated in subsequent analyses.

### 4.2.3 Other Neural Markers of Relapse

Apart from the activation of the right PIC, relapsers also evinced greater cluster deactivation: (1) left pars operculum of the inferior frontal cortex and precentral region; (2) right superior frontal regions; and (3) right postcentral region. Although these regions do not overlap per se with the findings of Farb, et al. (2010), they still might provide some clinical utility in understanding the contributants to relapse. Pre-post changes in functional activation of the foregoing clusters were not predictive of pre-post change in any clinically relevant constructs, though post-treatment activity was predictive of relapse status, which was to be expected considering these brain regions emerged from relapse status differences. Of the three, the left

inferior frontal and precentral cluster was the most related to depressive symptomatology; increased activation of this region across time predicted less sadness reactivity at post-treatment, while greater activation at post-treatment predicted more depressive symptoms and less body awareness. These negative outcomes could be the product of compromised emotion regulation strategies underlined by abnormal inferior frontal deactivation. This region has been linked to the deployment of cognitive control in regulating emotion (Ochsner, et al., 2004), and is thought to contribute to the reappraisal process by selecting content for reappraisal and eliciting inner speech to evaluate the significance of the content (Morawetz, Bode, Baudewig, Jacobs, & Heekeren, 2016). Similarly, the right superior frontal region has also been implicated in reappraisal (Falquez, et al., 2014; Frank, et al., 2014), so deactivations of the inferior and superior frontal clusters could necessarily reflect an inability to fully process dysphoric cues in an adaptive manner. Finally, although the postcentral gyrus has not been typically linked with depression or depressive relapse in the past, it has been implicated as a central structure for interoceptive awareness (Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004). As such, its deactivation may indicate that relapsers, especially those within the MBCT group, are further deactivating this structure to dissociate from their senses during sadness provocation in an effort to avoid emerging dysphoric mood. Alternatively, Fujino and colleagues (2014) showed that individuals diagnosed with MDD exhibited deactivations of the right somatosensory region in response to the pain of others, which the authors proposed could be indicative of a deficit in identifying with others. In the context of the current study, relapsers may have been far too overwhelmed with their own emotional state to empathize with the actors in the sad film clips.

Brain regions outside of the general relapse-specific clusters also emerged significant, including the left posterior and middle cingulate, right angular and middle occipital, and left middle temporal. Change in left middle cingulate signals was associated with many of the

clinical measures, predicting increased dysfunctional thinking across time, and greater sadness reactivity and depressive symptoms at post-treatment. Moreover, change in the right angular and middle occipital corresponded with increased sadness reactivity and depressive symptoms across time, and greater depressive symptoms at post-treatment. Like the postcentral gyrus, the middle cingulate cortex has been linked to empathy for others in pain (Lamm, Decety, & Singer, 2011), and MDD sufferers have been reported to deactivate this region during the perception of others' pain (Fujino, et al., 2014). As such, intervention groups might differ in how this cluster is engaged. When confronted with a sorrowful situation, MBCT participants might apply their skills by wholeheartedly accepting their dysphoric emotions and fully attending to others affected by the situation, hence the apparent increase in activation across time. Conversely, assuming relapsers drive this effect, it may reflect an individual's inability to remain detached from relatively minor and impersonal cues (e.g. a film clip) and instead succumb to the mood elicitation. As for CBWT participants, they might be exhibiting increased deactivation over time because their reappraisal skills are being utilized to lessen the impact of the dysphoric scene on their own mood by either reinterpreting the importance of the situation for themselves (e.g. "it's just a film clip"). The angular gyrus, on the other hand, is a hub of the DMN (Andrews-Hanna, Smallwood, & Spreng, 2014), and has been previously linked to alternating from first- to third-person perspectives (Ruby & Decety, 2004). With this in consideration, one would expect to find greater pre-post activation of the right angular and middle occipital in the CBWT group, when in fact it decrease across time. The angular gyrus has also been linked to episodic memory retrieval (Seghier, 2012), so CBWT participants may be inhibiting activity of this region to limit the number of personal memories that are elicited by the dysphoric cues. In contrast, MBCT participants might see an increase in this region despite its association with the DMN because of elevated decentering and metacognitive awareness post-treatment. By engaging in mindfulness

practices, one might become better able to adopt a third-person perspective supported by the angular gyrus without triggering other DMN structures.

In general, the activation of the left middle temporal, middle cingulate, and other co-activated structures, such as the superior frontal, was relatively stable for non-relapsers across intervention, while relapsers fluctuated greatly. Signal change across time in the foregoing clusters corresponded with increased pre-post dysfunctional attitudes, while the left posterior and middle cingulate specifically predicted greater depressive symptoms at post-treatment. Perhaps the most notable finding was that of the left middle temporal, as it was driven primarily by increased activation from pre- to post-treatment in MBCT relapsers, and was the only brain region differentiating MBCT from CBWT at post-treatment. This structure is a component of the linguistic-semantic network, and is involved in emotional encoding and retrieving of language (Onoda, Okamoto, & Yamawaki, 2009). In addition, the left middle temporal is implicated in moral cognition, theory of mind, and empathy (Bzdok, et al., 2012), and activity in this region in the current study likely reflected participant's empathy or understanding of others (i.e. actors in the films). For both left middle temporal and left posterior and middle cingulate, hyperactivation of these regions in the MBCT group may reflect a misapplication of acceptance that results in losing oneself in the emotions of another. Based on the median bar graphs for the aforementioned regions, the posterior and middle cingulate activity in the CBWT group appears to normalize at post-treatment, while activity in the left middle temporal plummets below baseline at post-treatment. As explained above, this may stem from a misapplication of reappraisal skills, wherein attempts to reappraise the dysphoric situation severely decrease one's ability to empathize with others, but also to connect with the situation in such a way as to fully process the emotional happenings and adaptively manage the situation.

## 4.3 Limitations

Before attempting to understand the findings from a wider perspective, some caveats and limitations of data interpretation of the current study must first be noted. First, most of the whole brain and correlational analyses were exploratory in nature, the latter of which was left uncorrected for familywise error and may have resulted in false positive associations. As such, these findings must undergo replication before one can confidently attribute these clinical indices to specific neural activations and deactivations. Second, the small number of relapsers limits the power and generalizability of findings to other potential relapsers. Third, treatment adherence and competency checks were not incorporated, and it is therefore difficult to say whether the results were not the product of clinicians veering away from the treatment manuals. Fourth, the film clips using during the sadness provocation task lacked personal relevance to the participants, and as such, may have activated neural regions implicated in empathy than in self-regulation. Although these findings are still clinically useful, it is expected that a personally relevant cognitive paradigm could have resulted in more pronounced effects or activated differential neural regions. Fifth, the behavioral outcome measures focused exclusively on aspects of depression and did not include any measures of more adaptive functions, such as acceptance and self-compassion. Inclusion of such measures could have further clarified the associative features of each brain region; for instance, a negative correlation between acceptance and postcentral activity would have provided additional support for the role of dissociation from perceptions in relapsers. Finally, current fMRI paradigms prevent researchers from determining which of the conditions comprised in constructing a contrast image are driving the differences between conditions. For example, if MBCT non-relapsers differ from relapsers at post-treatment in regards to MPFC activity in contrasts comparing reactivity to sad film clips versus reactivity to

neutral film clips, it is unknown whether this difference at post-treatment is driven by decreases in sadness processing or decreases in neutral processing.

## 4.4 Implications and Conclusions

The findings indicate that MBCT and CBWT did not differ drastically in their neural responder effects, and that any differences between the two appeared to be driven primarily by relapsers. This dovetails with the aforementioned statement that maintenance treatments may derive their therapeutic effects from stabilizing normalized behavioral and neural responses. However, the true differences may actually lie in functional connectivity than in the prominent activation or deactivation of structures per se. Further empirical investigations into the neural correlates of MBCT are needed to ascertain the role of the posterior insula and the medial prefrontal cortex in treatment, as the current findings did not correspond with those of a previous study into sadness provocation and mindfulness-based intervention (Farb et al., 2010). The differences in findings may stem from several factors, one of which is the difference in mindfulness-based interventions studied; whereas Farb and colleagues (2007; 2010) focused on MBSR, the current study instead opted for MBCT. Though major differences in neural reactivity were expected to generalize from one mindfulness-based intervention to another, it is possible that the differences between interventions, such as the emphasis on cognition and relapse prevention in MBCT, may drive very different therapeutic effects. To fully understand what behavioral and neural findings can be attributed to the mindfulness component or to other treatment factors, it would behoove clinical researchers to compare these similar practices and interventions.

It also appears that, in general, the clinical utility of maintenance treatments such as MBCT and CBWT is in stabilizing behavioral and neural reactivity to sadness provocation. From a neural standpoint, non-relapsers in both interventions show comparable responses across time,

while the neural patterns of relapsers is marked by extremes, either activating or deactivating functional clusters that are already within the range of normalcy. In addition to the emerging neural differences following treatment, relapsers show a persistent deactivation of the inferior frontal and precentral, right superior frontal, and right postcentral regions from pre to post-treatment. These unresponsive functional clusters may reflect the neural flipside of the 'rollback phenomena', where persistent maladaptive brain activity may also keep participants vulnerable to relapse and recurrence. This has major implications of treatment for both MBCT and CBWT. First, incorporation of neurobiological measures into treatment may provide clinicians with an alternative assessment tool that obviates the need for self-report and the inaccuracies stemming from response biases or a lack of psychological mindedness. If these persistent neural activations are indicative of the initiation of a rollback symptom phase even before clients are self-reporting substantive increases in depressive symptoms and their severity. Second, the findings encourage clinicians to be more cognizant of clients who may be attending therapy sessions and adhering to practice guidelines regularly, but are misapplying skills in such a way that provides immediate comfort from sadness reactivity in the short term but that may not be sustainable in the long term. An analogous emotion regulation strategy is that of distraction, which is preferred to cognitive reappraisal during encounters with high intensity stressors, but is thought to circumscribe long-term adaptive functioning, as it keeps individuals from fully processing and eventually reappraising recurrent stressors. Finally, the findings encourage clinicians to develop new practices or consider new ways of teaching the therapy material to these individuals to avoid misinterpretation or misapplication. Rather than simply quantifying practice according to, for instance, number of hours engaged in meditation or frequency of practice throughout the week, clinicians should consider assessing the *quality* of practice and understanding the process in which clients bring about the mindfulness state.

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