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How Mindfulness Training May Help to Reduce Vulnerability for Recurrent Depression: A Neuroscientific Perspective

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Abstract

This review investigates how recent neuroimaging findings on vulnerability for depression and the mechanisms of mindfulness may serve to inform and enhance the understanding that is guiding the use of mindfulness training in the prevention and treatment of recurrent and chronic depression. In particular, we review evidence suggesting that alterations in default-mode-network activity and connectivity represent a fundamental deficit underlying cognitive vulnerability for depression and explore the ways in which mindfulness meditation may reverse such alterations. Furthermore, we discuss findings from studies that have investigated the effects of mindfulness on emotion-regulatory capacities. These findings suggest mindful emotion regulation has a characteristic neural signature that is particularly conducive to therapeutic learning. We conclude that training in mindfulness has unique strengths for addressing neural mechanisms associated with cognitive vulnerabilities for recurrent and chronic depression and propose future lines of research to more effectively harness this potential.

Keywords

mindfulness, depression, neuroimaging, default-mode network, reconsolidation

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Major depression causes an enormous burden of disease for the affected individuals whose profound changes in mood prevent them from participating fully in their family, work, and social life, as well as for those around them and for society as a whole (Ferrari et al., 2013; Richards, 2011). What is perhaps most concerning is the fact that depression tends to follow an increasingly protracted course. Likelihood of recurrence increases with the number of previous episodes (Mueller et al., 1999; Solomon et al., 2000), and in many patients, symptoms persist, either on clinical or residual levels, over prolonged periods of time (Judd, Akiskal, & Maser, 1998; Paykel et al., 1995). Although the disorder is formally defined by its characteristic mood state and associated symptoms (American Psychiatric Association, 2013), more recent views have suggested that the pathology consists not so much of the mood state per se but an *increased tendency to enter into* and an *inability to disengage from this mood state* (Holtzheimer & Mayberg, 2011). Over repeated exposure, this tendency seems to become increasingly autonomous, thereby posing an important challenge to treatment.

Training in mindfulness has been introduced to the treatment of depression as a means of addressing the latent cognitive vulnerabilities that underlie these dynamics. Mindfulness-based cognitive therapy (MBCT; Segal, Williams, & Teasdale, 2002, 2013), which combines elements from cognitive therapy for acute depression with intensive training in mindfulness meditation, was

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specifically developed for prevention of relapse in patients with a history of recurrent depression. Since its introduction more than a decade ago, research has gathered promising evidence for the effectiveness of the program, consistent with a growing body of research that has demonstrated beneficial health effects of mindfulness meditation in general (Khoury et al., 2013). Findings from a number of randomized controlled trials have suggested that, although of little benefit in patients with one or two past episodes, MBCT significantly reduces risk for relapse in those with three or more previous episodes (Piet & Hougaard, 2011). To date, three large studies have reported effects that were comparable with those of continuing antidepressant medication (Kuyken et al., 2008; Kuyken et al., 2015; Segal et al., 2010). Furthermore, there is accumulating evidence for beneficial effects in patients with a chronic course of the disorder (Barnhofer et al., 2009; Eisendrath et al., 2008; Kenny & Williams, 2007; Strauss, Hayward, & Chadwick, 2012).

However, some recent trials have shown more ambiguous results. Two large trials have reported significant preventative effects only in subgroups of patients with recurrent depression: One trial (Segal et al., 2010) showed preventative effects only for patients with unstable remissions, and another (Williams et al., 2014) showed preventative effects only in patients with a history of early adversity. Furthermore, there are now a number of trials that, despite having achieved low rates of relapse, have failed to demonstrate significant advantages of MBCT over control treatments (Bondolfi et al., 2010; Meadows et al., 2014). Although these findings have suggested that mindfulness training has considerable potential to reduce risk in individuals who are most vulnerable, they also have shown that there is currently considerable variation in results. It seems important, therefore, to further refine our knowledge of how the intervention works in terms of understanding both the vulnerabilities that need to be targeted and the mechanisms through which these vulnerabilities may be reversed or reduced.

Recent initiatives have suggested that psychopathology may be more precisely described by using basic dimensions of psychological functioning and have stressed the importance of validating these dimensions across different layers, including neurobiological perspectives (Cuthbert & Kozak, 2013; Sanislow et al., 2010). The rationale of MBCT was almost exclusively developed from a cognitive understanding of the processes underlying relapse and maintenance of depression (Teasdale, 1999a, 1999b; Teasdale, Segal, & Williams, 1995), highlighting the role of maladaptive repetitive patterns of thinking and the fact that, with increasing numbers of episodes, such patterns can become increasingly habitual and easy to reactivate through even minor triggers, such as subtle changes in mood (Scher, Ingram, & Segal, 2005).

The aim of this review is to investigate how recent findings from neuroscience can enhance understanding of the ways in which mindfulness training can help in the prevention and treatment of recurrent and chronic depression. We begin by recapitulating the main aspects of the cognitive understanding of vulnerability and the cognitive mechanisms through which mindfulness training is assumed to change this vulnerability. We then review and discuss findings that relate to neural dynamics underlying reactivation and maintenance of maladaptive repetitive patterns of thinking and the ways in which mindfulness training may affect these dynamics before we investigate neuroscience findings that elucidate the neural signatures of mindful emotion regulation. On the basis of our review of findings from research on neural effects of mindfulness meditation, we suggest that mindfulness training is particularly suited to address imbalances in brain dynamics underlying cognitive vulnerability for depression and that mindful emotion regulation is particularly conducive for therapeutic learning. Finally, we outline potential new lines of research that arise from these suggestions and discuss implications for further development of mindfulness-based interventions.

The Cognitive Rationale Underlying MBCT

The suggestion to use mindfulness training in the prevention of relapse to depression was derived from a comprehensive new account of the cognitive processes involved in relapse and recurrence (Teasdale, 1999a, 1999b; Teasdale, Segal, & Williams, 1995). Consistent with the cognitive theory of depression by Beck, Rush, Shaw, and Emery (1979), the rationale for MBCT acknowledged the importance of the content of negative thoughts and beliefs but included a particular emphasis on the characteristics and qualities of the thinking *process*.

In his articles outlining the theoretical rationale for MBCT, Teasdale (1999a, 1999b) had described how negative repetitive thinking, which often takes the form of *rumination* about the causes and consequences of one's negative mood (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008), not only reinforces the schemata or internal depressogenic models that guide negative interpretations of events but also activates depressive body states that further increase the likelihood of depressive thinking, thus setting up a mutually reinforcing process that he referred to as *depressive interlock*. It was assumed that repeated engagement in this process would establish habitual tendencies to engage in maladaptive patterns of thinking and strengthen their association with negative mood (Segal, Williams, Teasdale, & Gemar, 1996).

Consistent with this view, research has demonstrated that, in previously depressed patients, the negative

thinking patterns that were predominant during episodes of depression could be easily reactivated when patients were in recovery (Scher et al., 2005). In fact, experiments have shown that subtle triggers, such as small changes in mood, could reinstantiate not only dysfunctional beliefs (Miranda & Persons, 1988) but also whole modes of processing characterized by a range of different cognitive processes (Beck & Haigh, 2014). The degree to which patients showed such *cognitive reactivity* predicted later relapse, which stresses the central role of these mechanisms for relapse to depression (Segal et al., 2006).

Training in mindfulness—defined as "the awareness that emerges through paying attention on purpose, in the present moment, and non-judgmentally to the unfolding of experience moment by moment" (Kabat-Zinn, 2003, p. 145)—was introduced as a means of helping participants to become better able to recognize and disengage from maladaptive patterns of responding to negative mood (Segal et al., 2002). Teasdale (1999a) suggested that a mindful mode of processing, in which contents are processed experientially rather than conceptually, would allow individuals to see negative thoughts and feelings as transient events in the mind and, through this metacognitive insight, to change their relation to them, thereby preventing the processes that give rise to the self-perpetuating loop of depressive interlock. Furthermore, it was assumed that repeated instances in which individuals related to difficult experiences with an open and acceptant stance (i.e., being willing to tolerate and even "turn toward" experience rather than striving to change it), rather than engaging the usual attempts at solving the existing problem (conceptually based rumination and avoidance), would gradually shape the internal schematic models that are guiding maladaptive responses to negative mood, thereby replacing these responses with more adaptive ones and, thus, reversing established cognitive vulnerabilities.

Consistent with the rationale of the treatment, research findings have shown that training in mindfulness can indeed increase patients' ability to decenter and that such increases in decentering are associated with reductions in risk for relapse (Bieling et al., 2012). Furthermore, there is evidence that treatment-related changes in symptoms are mediated by reductions in maladaptive rumination (Heeren & Philippot, 2011). However, despite some positive findings (Raes, Dewulf, Van Heeringen, & Williams, 2009), evidence for effects on cognitive reactivity is currently weak; the most conclusive study to date has reported slight increases rather than decreases in cognitive reactivity after MBCT (Kuyken et al., 2010). It remains unclear, therefore, how far the program can reverse the latent vulnerabilities that are driving maladaptive responses to negative mood. Further research is needed to test whether standard mindfulness-based interventions can achieve such effects and how to adapt the program if necessary. However, cognitive studies are limited in their ability to assess latent vulnerabilities, and particularly the degree to which individuals may be prone to shift into and maintain a maladaptive mode of processing, beyond the use of indirect indicators, such as cognitive reactivity. Neuroscience research may offer ways of assessing such characteristics more directly.

Recent advances in the investigation of interactions of distributed brain networks have provided opportunities to gain information about the unfolding of complex processes and their conceptualization in terms of global states and modes (Bressler & Menon, 2010; Menon, 2011; Smith et al., 2012). In particular, research on the "default-mode" network (DMN; Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001) and its relationship to other networks of the brain has offered an important window into processes underlying a broad range of internal mentation and, in particular, spontaneous thought (Callard & Margulies, 2014; Smallwood & Schooler, 2006; Teasdale, Dritschel, et al., 1995), a domain that is of central importance for understanding the processes that lead to increases in cognitive vulnerability for depression as individuals repeatedly suffer from new episodes. Research into functional connectivity and resting-state dynamics of these networks (Allen et al., 2014; Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995; Chang & Glover, 2010; M. D. Fox & Raichle, 2007; Hutchison, et al., 2013) has offered insights into predispositions toward particular forms of processing and, thus, is relevant with regard to latent vulnerabilities.

Similarly, there is now a considerable body of research that has elucidated the effects of meditation training on brain functioning and structure. Evidence has suggested that meditation practice may help induce increased plasticity in the brain (Lutz & Greischar, 2004), and intensive meditation practice has been shown to be associated with structural changes in key areas implicated in the regulation of attention and emotion (K. C. Fox et al., 2014; Hölzel, Lazar, et al., 2011). Although this indicates that mindfulness has considerable potential for reversing vulnerability on the neural level, there has been relatively little effort so far to explicitly relate neural mechanisms to the clinical application of mindfulness. Furthermore, research into the neural mechanisms of mindful emotion regulation has provided information that is relevant for the understanding of how best to instigate therapeutic learning and may offer helpful insights for increasing effectiveness of mindfulness-based interventions. We first turn to the investigation of how findings on resting-state networks and their dynamics may inform the understanding of latent vulnerability before we explore neuroscience findings relevant to the understanding of the mechanisms of mindfulness.

DMN Activity, Connectivity, and Dynamics and Their Alterations in Depression

Recent progress in the understanding of the neural correlates of spontaneous thinking in general, and maladaptive thinking patterns underlying vulnerability for depression more specifically, has arisen particularly from research on the dynamics, function, and connectivity of the DMN. The DMN consists of a set of brain regions, including the medial prefrontal cortex, posterior cingulate/retrospinal cortex, and the left and right inferior parietal lobules (Buckner, Andrews-Hanna, & Schacter, 2008; Whitfield-Gabrieli & Ford, 2012), and, less consistently identified, the medial temporal lobes and hippocampal formation (Buckner et al., 2008), that show consistent increases in activity during seemingly passive, internally directed states and decreases in activity during externally directed task performance (Raichle et al., 2001; Shulman et al., 1997), as well as intrinsic functional connectivity (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Greicius et al., 2003). Because of the decrease in activation in its regions during task performance, the DMN is sometimes also referred to as a task-negative network (TNN), which is contrasted to a task-positive network (TPN), which is active during goal-directed processes and encompasses portions of the dorsolateral prefrontal cortex, dorsal anterior cingulate cortex, the intraparietal sulcus, and middle temporal area, among other regions (Cabeza & Nyberg, 2000; Corbetta & Shulman, 2002; Sonuga-Barke & Castellanos, 2007). The DMN is antagonistically coupled with external attention networks composed by the TPN, and normal activity during rest involves a coordinated switching between the TNN and the TPN. Analyses of resting-state functional connectivity have demonstrated that, although there are spontaneous correlations within the networks, activity between the networks is predominantly anticorrelated (M. D. Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; M. D. Fox et al., 2005; Fransson, 2005; Kelly, Uddin, Biswal, Castellanos, & Milham, 2007; Margulies et al., 2007).

However, antagonistic effects between the networks have also been shown to vary (Chang & Glover, 2010). Studies that have investigated activation and deactivation of the networks have demonstrated that, although TPN activity increases with cognitive load and task difficulty (Cabeza & Nyberg, 2000; Corbetta & Shulman, 2002), spontaneous activity within the DMN can persist throughout demanding task conditions. In fact, it has been argued that DMN suppression is vital for effective cognitive performance (Anticevic et al., 2012). In healthy individuals, increased DMN activity during tasks has been shown to be associated with likelihood of attentional lapses and performance errors (Anticevic, Repovs, Shulman, & Barch, 2010; Cole, Yarkoni, Repovs, Anticevic, & Braver, 2012; Daselaar, Prince, & Cabeza, 2004; Kelly et al., 2008), which suggests that suppression of DMN activity during engagement in external, cognitively demanding tasks is necessary to disengage from internal mental processes that would otherwise interfere with performance.

Studies of psychological correlates have shown that DMN activity is associated with a wide range of internal mentation that involves self-referential processing: remembering one's past, planning one's future, and forming one's beliefs with focus on oneself as a shared theme across these activities (Buckner et al., 2008). It is important, however, that the quality of the self-referential thinking indexed by the DMN differs from active self-referential thinking in that it is more akin to spontaneous mind wandering (Whitfield-Gabrieli et al., 2010). In fact, DMN activity has been shown to be a characteristic correlate of mind wandering (Mason et al., 2007), thereby highlighting the spontaneous or automatic nature of the mental processes associated with the network, a characteristic that is reminiscent of the nature of ruminative processes assumed to be at the core of cognitive vulnerability for relapse to depression. Although mind wandering per se may not be problematic, and may in fact sometimes have positive effects, such as supporting creativity (Schooler et al., 2014), it has been suggested that such spontaneous stimulus-independent thought can easily turn into maladaptive repetitive thinking if content is negative and engagement in the process becomes rigid and dominant (Teasdale, Dritschel, et al., 1995).

Consistent with this view, results from research in depressed patients have shown a number of alterations in both DMN connectivity and activation. In particular, there is evidence for increased connectivity between regions of the DMN and the subgenual anterior cingulate (Berman et al., 2011; Berman et al., 2014; Greicius et al., 2007), a region that is hyperactive during the depressive state and plays an important role in modulating autonomic and visceral responses during the processing of sadness, fear, and stress (Mayberg, 1997; Phan, Wager, Taylor, & Liberzon, 2002). Of note, functional connectivity between the DMN and the subgenual cingulate has been shown to be positively correlated with the duration of the current episode (Greicius et al., 2007) and self-reported tendencies toward rumination and brooding (Berman et al., 2011). Research that has investigated state changes (Berman et al., 2014) has shown that when individuals think about negative events in their life, compared with unconstrained rest, functional connectivity between the posterior cingulate and the subgenual cingulate cortex significantly increases.

Other research in patients who suffer from current depression has shown increased resting-state functional connectivity between the DMN and a region of the dorsal

medial prefrontal cortex referred to as the dorsal nexus (Sheline, Price, Yan, & Mintun, 2010). The dorsal nexus is assumed to serve as an intersection point for different brain networks, and findings have indicated hyperconnectivity between this region and regions of the TPN implicated in cognitive control, as reflected by a seed region in the dorsolateral prefrontal cortex, and an affective network, as reflected by a seed region in the subgenual anterior cingulate cortex. The degree of connectivity between this dorsal nexus and the three networks has been shown to be strongly related to the severity of depression. Adaptive functioning requires a delicate balance between cognitive control and affective processing, and increased connectivity between networks and the resulting imbalances may account for a broad range of dysregulations and cognitive deficits in depression, which facilitates attentional shifts toward self-focus and undermines effective task performance (Sheline et al., 2010).

Further evidence for brain-network imbalances has come from research that has investigated task-related deactivations of the DMN in depressed patients. Studies on brain activation during both passive viewing and reappraisal or rating of emotional pictures have shown that, compared with healthy control individuals, depressed patients show significantly increased and sustained activation of widely distributed regions of the DMN regions, which indicates deficits in deactivation of DMN in depression (Grimm et al., 2009; Sheline et al., 2010). The degree to which DMN activity persisted during task performance has been shown to be significantly associated with the severity of depression (Grimm et al., 2009).

More recent studies have suggested that such alterations are also visible in individuals who are currently free of symptoms but carry a high risk for depression or relapse to depression. Norbury, Mannie, and Cowen (2011) compared young people who had never suffered from depression, but who had a biological parent suffering from major depression, with control individuals whose parents did not suffer from depression and found increased connectivity between widely distributed DMN structures and the dorsomedial prefrontal cortex, thus replicating earlier findings from research in depressed patients (Sheline et al., 2010). A recent investigation of task-induced deactivation of the DMN in previously depressed patients who were currently in remission showed that, similar to depressed patients, previously depressed patients differed from healthy control individuals by showing reduced deactivation of the DMN during tasks (Nixon et al., 2014).

On the basis of these and similar findings, it has been argued that alterations in DMN connectivity and imbalances in DMN dynamics may represent a fundamental deficit underlying cognitive vulnerability for depression and, in particular, increased tendencies to engage in maladaptive ruminative responses to negative mood (Marchetti, Koster, Sonuga-Barke, & De Raedt, 2012). In fact, studies in depressed patients in which researchers have looked more specifically into the relation between DMN dynamics and rumination have shown a significant positive correlation between the degree to which DMN activation dominates over activation of TPNs during rest and maladaptive depressive rumination (Hamilton et al., 2011). These findings are important, given that they suggest that prevention of depression would not only require that patients be taught how to respond to difficult and stressful situations but also necessitate a more fundamental change in attentional functioning and rebalancing of learned tendencies to engage in a particular mode of processing that becomes obvious during rest but is likely to influence cognitive functioning across many situations in life—a view that is consistent with the rationale of mindfulness-based interventions.

Effects of Mindfulness Meditation on DMN Dynamics and Connectivity

How might mindfulness training help to change these neural mediators of vulnerability? There is evidence to suggest that mindfulness training may be particularly suited to strengthen regions implicated in the regulation of dynamics between the DMN and TPNs. A central region in this context is the right anterior insular cortex, which together with the anterior cingulate cortex and a number of other structures, including the amygdala, thalamus, substantia nigra, and ventral tegmental area, forms a network, referred to as the salience network. This network functions to identify the most relevant stimuli at any given time point and to guide behavior on the basis of their evaluation (Seeley et al., 2007). Research has shown that the right anterior insular cortex is critically and causally implicated in switching between the DMN and the executive control network (Sridharan, Levitin, & Menon, 2008), a part of the TPN. Consistent with this view, findings from research in depressed patients have shown that increased activation in the right fronto-insular cortex reliably preceded increases in activity of the TPN (Hamilton et al., 2011).

A recent meditation study (Hasenkamp, Wilson-Mendenhall, Duncan, & Barsalou, 2012) has illustrated how the different mental operations involved in focused-attention meditation engage different networks and the skill to switch between them. Experienced meditators were asked to engage in a breath-focused meditation while undergoing functional MRI scanning and to signal, by pressing a button, whenever they had noticed that their mind had wandered. Button presses served as a

reference point for the construction of intervals to map onto the cognitive cycle of mind wandering, awareness of mind wandering, shifting of attention, and sustaining attention that is characteristic of focused-attention meditation. Analyses revealed patterns of activity that demonstrated dominance of the DMN during mind wandering and dominance of the salience network during awareness of mind wandering, whereas the executive network was most active during shifting and sustaining attention. It is important that activations during these phases were modulated by lifetime meditation practice, thereby providing evidence that consistent meditation training can increase the ability to flexibly engage relevant networks. These findings have suggested that focused-attention meditation can specifically train the ability to switch between networks and, thus, may be particularly suited to redress imbalances in network dynamics.

Although there are no studies yet that have investigated the effects of mindfulness training on network imbalances in individuals who are depressed or those at increased risk for depression, there is evidence from studies in healthy control individuals to suggest that meditation practice entails changes in the very regions involved in regulating the earlier described dynamics, namely, the anterior insula and the anterior cingulate cortex. The anterior insula and the anterior cingulate cortex play an important role in the evaluation of task performance and the initiation of action after errors, and focused-attention-meditation practices, with their demand of monitoring attention against an intended focus, such as the breath, represent an almost prototypical task to engage these regions (Cahn & Polich, 2006). Consistent with this view, structural imaging research has demonstrated that expert meditators show significantly greater cortical thickness in the anterior cingulate (Grant, Courtemanche, Duerden, Duncan, & Rainville, 2010) and the right anterior insula (Hölzel, Carmody, et al., 2011; Lazar et al., 2005) than do control individuals. Research on white-matter integrity has reported changes in the region of the anterior cingulate after only 11 hr of practice (Tang et al., 2010).

Resting-state connectivity is modulated through prior learning (Hasson, Nusbaum, & Small, 2009; Lewis, Baldassarre, Committeri, Romani, & Corbetta, 2009; Stevens, Buckner, & Schacter, 2010), and it is conceivable, therefore, that repeated training and engagement in a mindful mode of processing may translate into changes in resting-state connectivity of the DMN. Preliminary support for this assumption comes from a study by Taylor et al. (2013) that showed that, compared with healthy novices, expert meditators have decreased resting-state connectivity between the ventromedial prefrontal cortex and other regions, including the dorsomedial prefrontal cortex and regions of the right temporal cortex; that is, expert meditators showed weaker connectivity between regions involved in self-referential processing and emotional appraisal (however, see also findings by Jang et al., 2011, that showed increased connectivity among DMN nodes in experienced meditators).

Altogether, these findings have suggested that mindfulness meditation, and particularly focused-attention meditation, can help practitioners to more effectively recruit regions of the salience network involved in cognitive control and bodily awareness and may thereby increase individuals' ability to more flexibly switch between DMN and TPN activity and related modes of processing. Evidence that expert meditators show reduced resting-state connectivity with regions involved in self-referential thinking (Taylor et al., 2013) has suggested that, with continued practice, effects may translate beyond the state of meditation, thereby reversing alterations in DMN connectivity that are characteristic of depression, although such effects may require considerable amounts of practice. In a preliminary study in healthy control individuals, researchers did not find differences in resting-state connectivity between participants of an 8-week mindfulness-based intervention and participants who had served as a wait list control (Kilpatrick et al., 2011).

Although general shifts toward reduced DMN dominance and increased flexibility in switching between different modes of functioning may be helpful in reducing the overall likelihood of engagement in maladaptive thinking patterns, it is also important to keep in mind the potential adaptive functions of self-focused thinking in response to negative mood and depression. A recent review and meta-analysis (Pizzagalli, 2011) has shown that, across a broad range of interventions for depression, better treatment responses are strongly and robustly related to increased resting activity in the rostral anterior cingulate cortex, which is a region that serves as a hub for a subsystem of the DMN that becomes active when people think about their present state, make affective decisions (Andrews-Hanna, Smallwood, & Spreng, 2014), or resolve emotional conflict (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006). This finding has suggested that in addition to helping patients become better at disengaging from maladaptive forms of self-focused thinking, treatments need to help patients to become better at engaging reflective processes in an adaptive way.

This is a particular challenge, given the automatic biases toward maladaptive processing that are characteristic of depression and vulnerability for depression. In a recent study on the relation between reflection and depressive symptoms, we found that, in previously depressed patients, reflection was significantly associated with increased levels of depression unless individuals had high levels of mindfulness and were able to process autobiographical content

with a high level of specificity, in which case reflection was associated with adaptive effects (Brennan, Barnhofer, Crane, Duggan, & Williams, 2015). Neuroimaging research on the brain regions that become active during controlled self-focus has shown considerable overlap with the DMN, including, in particular, the medial prefrontal and posterior cingulate cortex regions. However, there is an important difference in that the spontaneous mental processes classically associated with DMN activity lack involvement of the dorsal medial prefrontal cortex. Meditation research has shown that the dorsal medial prefrontal cortex is selectively activated during meditation (Hölzel et al., 2007); cortical thickness in this region has been shown to be significantly associated with the amount of previous meditation practice (Lazar et al., 2005). Furthermore, studies of functional connectivity have revealed stronger coupling in experienced meditators between the posterior cingulate, dorsal anterior cingulate, and dorsolateral prefrontal cortex, all of which are implicated in self-monitoring and cognitive control (Brewer et al., 2011). It seems possible, therefore, that, by strengthening cognitive control, mindfulness training may help patients to engage self-focused thinking more adaptively.

Mindful Emotion Regulation

As individuals become more adept at meditation during the course of mindfulness-based interventions, the balance of practices shifts from focused-attention meditations, in which they learn to sustain the focus of their attention on an object, such as the sensations of the breath or body sensations more generally, to open monitoring, in which practitioners rest in a reflexive awareness of whatever experiences arise, observing their phenomenal quality, intensity, emotional tone, and potential relations to particular cognitive schemata and themes (Lutz, Slagter, Dunne, & Davidson, 2008). Open-monitoring practices are assumed to heighten awareness of current experience while at the same time reduce emotional and cognitive reactivity (Lutz et al., 2008).

With continuing practice, individuals increasingly recognize repeatedly occurring themes, a process that can be helped by labeling experiences during the meditations, and explicitly relate to these themes and their emotional and bodily resonances with openness and acceptance. Approaching difficulties with openness and acceptance is a defining characteristic of the mindfulness approach and, from a clinical perspective, is assumed to be critical for therapeutic modification of previously established patterns of responding. Imaging work is beginning to elucidate the neural signatures of these regulatory processes and how they might counter deficits in individuals who are vulnerable to recurrent depression.

Neural models of emotion regulation in depression

Difficulties in regulating negative emotions are a hallmark of depression. Neural models of depression follow the general view that these difficulties arise as a consequence of a combination of hyperactivity in limbic areas and insufficient controlling influences from prefrontal regions (Mayberg, 1997); more recent accounts have highlighted the importance of differentiating between functional abnormalities in different voluntary and automatic emotion regulatory subprocesses (Phillips, Drevets, Rauch, & Lane, 2003a, 2003b; Phillips, Ladouceur, & Drevets, 2008). In a recent review, Rive et al. (2013) suggested that depressed patients show reduced activity in lateral prefrontal cortex during explicit voluntary control of emotional experience, whereas during automatic stages of emotion regulation, depressed patients seem to rely on additional recruitment of lateral prefrontal regions. Disner, Beevers, Haigh, and Beck (2011) have outlined how such imbalances may relate to elements of the cognitive model of depression. They suggested that increased activity in the amygdala and other limbic structures contributes to the activation of negative schemata as well as negatively biased attention, processing, and memory, whereas increased activity in the medial prefrontal cortex and decreased activity of the dorsolateral prefrontal cortex are assumed to reflect deficits in cognitive control that contribute to the maintenance of biased processing. It has been suggested that psychotherapeutic approaches, such as cognitive-behavioral therapy, counter limbic hyperactivity by increasing prefrontal control. Consistent with this suggestion, results from a recent meta-analysis of neuroimaging findings in depression showed that treatment effects are indeed visible mostly in frontal regions, especially lateral frontal regions, whereas dysregulations in subcortical regions appear to be relatively insensitive to treatment (Graham et al., 2013). This latter result would suggest that limbic hyperactivity might be more likely to persist as a vulnerability, possibly reflecting reflecting an increased potential for cognitive reactivity to negative mood.

Neural mechanisms of mindful emotion regulation

Neuroimaging research has illustrated how verbal techniques may serve to support adaptive regulation of emotions. The simple act of labeling the affect of facial expressions and, thus, encapsulating the emotional meaning on a conceptual level, has been shown to be associated with increases in prefrontal control over limbic regions and reduced amygdala response (Creswell, Way, Eisenberger, & Lieberman, 2007). It is interesting that this

effect was moderated by dispositional mindfulness—higher self-reported mindfulness levels were associated with both reduced amygdala activation and increased prefrontal cortex activation during affect labeling—which suggests that individuals who are high in mindfulness may be able to more effectively downregulate negative emotions. Consistent with this finding, results from research that investigated the effects of mindfulness-based interventions has provided evidence for increases in emotion-regulatory capacities. Research on responses to negative self-beliefs in patients with social phobia has demonstrated that patients showed reduced amygdala responses after an 8-week training in mindfulness-based stress reduction (MBSR; Goldin & Gross, 2010). In a recent study on the effects of MBSR in patients suffering from generalized anxiety disorder, Hölzel et al. (2013) used the same affect-labeling task as used by Creswell et al. (2007) and found that, after the training, participants in the mindfulness group showed significantly reduced amygdala activation together with significant increases in ventrolateral prefrontal regions while viewing the faces. Other research has demonstrated relations between changes in perceived stress after training in MBSR and reductions in gray-matter density in the right amygdala (Hölzel et al., 2010).

These findings are consistent with the suggestion that mindfulness-based interventions may serve to counter increased limbic activity and reduced prefrontal control. Yet the mechanisms through which such normalization is achieved are likely to differ from those of psychotherapeutic techniques that focus on verbal techniques to support the reappraisal of negative thoughts and feelings. In their study investigating changes in patients with generalized anxiety disorder, Hölzel et al. (2013) found that connectivity between the amygdala and several regions of the prefrontal cortex, including bilateral dorsolateral and dorsomedial regions as well as the dorsal anterior cingulate cortex, changed from negative coupling, consistent with an inhibitory influence of prefrontal regions on limbic activity, to positive coupling, suggesting synchrony in activity. More importantly, the strength of the association was negatively correlated with the level of anxiety symptoms at the end of treatment; that is, increased positive coupling between the amygdala and regions of the prefrontal cortex was associated with lower symptoms (see Fig. 1 for functional-connectivity results). Mindfulness practices specifically train participants to observe physical and emotional responses with an open and allowing attitude, and Hölzel et al. suggested that the positive coupling observed reflects an open and acceptant monitoring of arousal and other internal events as compared with attempts at regulating affect that would be expected to result in negative coupling. An important vehicle for the cultivation of acceptance in mindfulness-based interventions is bodily awareness. Participants in MBCT are encouraged to relate to negative emotions by observing, with openness and curiosity, the changing physical sensations that come with the emotions. Research has shown that, compared with wait list control individuals, participants who received MBCT showed greater recruitment of right-lateralized somatosensory and visceral areas in response to negative mood induction (Farb et al., 2010), an effect that was associated with lower levels of depressive symptoms. Consistent with the psychological model of mindfulness, results from neuroimaging studies thus have shown a characteristic regulatory signature reflected in increased recruitment of viscerosomatic regions and relative abstinence of inhibitory influences from prefrontal regions on limbic activity. This signature is significantly different from the signatures of other verbal interventions as seen, for example, in the neural effects of affect labeling (Torrisi, Lieberman, Bookheimer, & Altshuler, 2013).

Why might this particular regulatory signature be advantageous? Bringing acceptance to difficult experiences and observing them in a mindful way is counterintuitive and requires considerable practice, yet it may be exactly because of these characteristics that mindfulness is particularly suited for transforming maladaptive cognitive habits underlying risk for depression. If, as the cognitive account of recurrent depression suggests, vulnerability arises from past learning and its reflection in memory networks or schemata, then effective reduction of risk for relapse to depression requires learning to alter and replace associations between negative mood and automatic tendencies to react maladaptively with other more adaptive responses. Although the training of more adaptive responses, such as decentering, might be helpful to reduce the likelihood of vulnerability processes to escalate, the reduction of latent vulnerability eventually requires the modification of the very memory structures that guide automatic maladaptive responses.

Recent memory research has produced findings that have important implications for the understanding of therapeutic processes of change. It is commonly accepted that memory formation occurs as a result of changes in synaptic efficacy, and researchers have increasingly detailed the molecular mechanisms involved in consolidation (Tronson & Taylor, 2007) and differentiated between an early transient and a later stabilized phase that is dependent on protein synthesis (Suzuki et al., 2004). Although it was previously assumed that memories, once they have undergone consolidation, remain consolidated, it has now become obvious that memory retrieval can return a memory to a transient state of instability from which the memory is then stabilized again (Nader & Einarsson, 2010; Nader, Schafe, & LeDoux, 2000), a process that is referred to as reconsolidation, and during which it can be modified, a process that is referred to as memory updating.

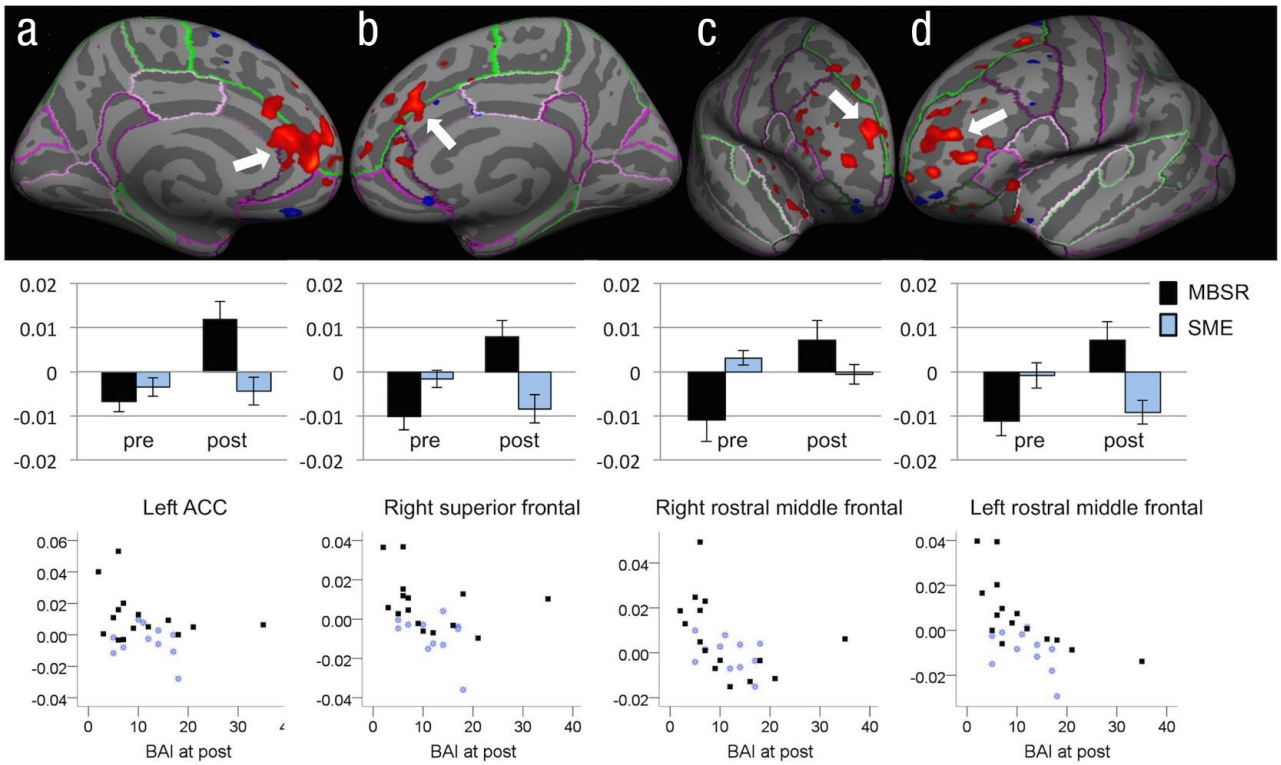

Fig. 1. Changes in functional connectivity between the seed region in the right amygdala and several regions in the frontal cortex from pre- to postintervention in patients with generalized anxiety disorder who underwent a mindfulness-based stress reduction (MBSR) program (n = 15) and participants in an active control condition that included stress management education (SME; n = 11). The top row shows anatomical location displayed on an inflated surface with FreeSurfer cortex parcellations, the middle row shows regression coefficients extracted from the clusters from the MBSR (black) and SME (blue) participants at pre- and postinterventions, and the bottom row shows scatter plots of regression coefficients and Beck Anxiety Inventory (BAI) scores for MBSR and SME participants at postintervention for the left rostral anterior cingulate cortex (ACC; Column A, pre- to postincrease in connectivity: p = .0002; correlation with BAI scores: ρ = −.229, n.s., uncorrected), right superior frontal cortex (Column B, pre- to postincrease: p = .04; correlation: ρ = −.470, p = .015), right rostral middle frontal cortex (Column C, pre- to postincrease: p = .03; correlation: ρ = −.572, p = .002), and left rostral middle frontal cortex (Column D, pre- to postincrease: p = .01; correlation: ρ = −.646, p = .001). Error bars represent standard errors. Reprinted with permission from Hölzel et al. (2013).

Reconsolidation offers a considerable promise for the treatment of emotional disorders. If memories involved in guiding maladaptive responses to emotional cues could be rewritten to include more benign associations, this would lead to permanent reductions in vulnerability. In a seminal study to explore this possibility, Schiller et al. (2010) used reconsolidation as an updating mechanism to alter previously conditioned fear memories. Individuals who had learned a conditioned fear response through pairing of a previously neutral stimulus with mild electric shocks were allocated to extinction training after either reactivation of the memory through presentation of the conditioned stimulus within the reconsolidation window, extinction training outside of the reconsolidation window, or extinction training without reactivation. Although extinction was successful in all groups, later tests showed that only those participants in whom extinction training took place within the reconsolidation window did not show spontaneous fear recovery (i.e., reemergence of the extinguished conditioned response), an effect that remained even when participants were tested 1 year after the initial test.

These findings clearly have demonstrated the advantages of updating over extinction learning without reactivation wherein the problematic memory remains unchanged, and may therefore become dominant again at later points in time, thereby suggesting important potential for improvement in the treatment of disorders that are characterized by problematic cue-response associations. In fact, evidence for significant and sustained effects of treatment using reconsolidation and updating mechanisms is now emerging in a number of domains, including the treatment of posttraumatic stress disorder (Brunet et al., 2011; Menzies, 2012). In the field of addictions (Saladin et al., 2013; Xue et al., 2012), these principles have been used for updating of cue–substance-use relations, an application that follows a rationale similar to that which guides the argument for the use of updating techniques for modifying associations between

negative mood and maladaptive patterns of thinking in depression.

MBCT uses mindfulness techniques that are particularly conducive to the use of reconsolidation and updating mechanisms. Although openness to difficult experiences is a guiding principle in all mindfulness-based interventions, MBCT has a particular focus on practices in which participants are explicitly instructed to hold in mind difficult situations or concerns. As participants observe the thoughts, feelings, and body sensations that come with difficulties, relevant memories are activated on a number of levels of representation while, at the same time, cultivation of acceptance and openness toward these experiences introduces a new response that is incompatible with previously established patterns. In patients with high levels of vulnerability, ruminative and avoidant responses to negative thoughts and feelings are highly habitual, and relating to such experiences with openness and acceptance is likely to be associated with initial discomfort and unease. Yet as individuals continue to observe their experience with a stance of openness and acceptance, it is often possible for them to see that negative thoughts and feelings are transient and constantly change in their quality, thus offering both new information and new experiences in relating to difficulties that potentially allow updating of their meaning.

Research on boundary conditions for reconsolidation has suggested that updating is particularly likely to occur when new learning violates predictions from previously established contingencies (Tronson & Taylor, 2007). From this perspective, the contrast between discomfort that arises when difficult themes, and the negative thoughts and feelings that accompany them, are held in mind in an open and allowing stance and a "new encoding state," in which practitioners experience a different relation to the difficult experience, may increase the likelihood for updating to occur. It is interesting that a recent study into the neural signatures of reconsolidation processes showed that reactivation of emotional memories is characterized by increased activity in the amygdala (Schwabe, Nader, Wolf, Beaudry, & Pruessner, 2012), which suggests that, at least within limits, such activation, and therefore the regulatory signature of mindfulness that allows for such activation to remain, may indeed be particularly conducive to updating.

Recent advances in the treatment of acute depression have emphasized the importance of such mechanisms, particularly in the treatment of chronic and recurrent depression. Work by Hayes, Laurenceau, Feldman, Strauss, and Cardaciotto (2007) on exposure-based therapy for depression has illustrated how effective treatments often follow a cubic trend in which temporal destabilizations provide a basis for modification to occur. MBCT includes techniques that are particularly suited for the use of reconsolidation principles and should thus have great potential to change associative memory structures underlying cognitive reactivity. Yet current findings on whether the training can reduce cognitive reactivity, an indicator of the strength of association between negative mood and maladaptive patterns of thinking, remain inconclusive. It is possible that inconsistencies are due to variations in exposure, given that practices are designed so that participants relate to what arises spontaneously during practices. The degree to which participants have exposures to difficult materials can therefore vary considerably. Furthermore, practices in which participants are explicitly invited to explore difficult experiences require advanced skills. In a study in which they compared responses to emotionally laden stimuli in groups of meditators with high or low levels of expertise, Taylor et al. (2011) found that novice meditators showed less amygdala activity, whereas expert meditators showed decreased activation of areas involved in self-referential processing. Although mindfulness practice thus appears particularly suited to use principles of reconsolidation, it is possible that this potential may remain underused or require more focused or extensive training.

Conclusions and Outlook

Studies of its cognitive mechanisms of action have confirmed that MBCT works by helping participants become better at recognizing and disengaging from maladaptive patterns of thinking (Bieling et al., 2012; Kuyken et al., 2010), a strategy that is predominantly remedial in nature, yet there is currently little evidence to support the assumption that the treatment can reduce latent vulnerability. Future research will be able to address this question more directly by investigating effects on neural indicators of vulnerability. In particular, researchers will have to investigate whether mindfulness training can reverse alterations in connectivity between the DMN and other networks involved in cognition and affect as reported in depressed patients (Sheline et al., 2010) and individuals who are at high risk (Norbury et al., 2011) and whether the training can reduce deficits in DMN suppression that research has shown to be characteristic of currently depressed (Grimm et al., 2009) and remitted patients (Nixon et al., 2014). Researchers focused on DMN dynamics will have to test whether the training can reduce DMN resting-state dominance, given previous findings that have related DMN dominance and tendencies toward rumination; although it is important to keep in mind in this latter context that current findings are exclusively from studies with patients who are currently suffering from depression. Further research is needed to demonstrate that such alterations remain as latent vulnerabilities when patients are in remission.

An important aspect of intervention studies on the effects on DMN alterations will be to explore the amounts and levels of practice that are needed to bring about such changes and to investigate potential moderating factors. Alterations in resting-state DMN dynamics and connectivity are likely to be an expression of highly engrained cognitive habits. Although there is evidence to suggest effects of mindfulness practice on DMN connectivity from studies in expert meditators (Taylor et al., 2013), preliminary results from research in healthy control individuals (Kilpatrick et al., 2011) has suggested that alterations may require amounts of practice to go beyond those offered by standard mindfulness-based interventions. Researchers who aim to produce such changes may thus have to increase emphasis on the cultivation of a continuous meditation practice. In fact, further development of interventions aimed at reducing vulnerability for depression may benefit from research into trajectories of change over different amounts of practice to clarify potential effects of mindfulness at different stages. Although effects on effectiveness of the salience network may be observable after short periods of practice (Tang et al., 2010), thereby strengthening capacity for remedial strategies, it is conceivable that it may take considerably longer for effects to translate into changes in resting-state connectivity and dynamics.

MBCT is a relatively brief intervention to address vulnerabilities that have developed over considerable periods of time, and although mindfulness meditation combines training of mental capacities with the cultivation of a particular stance towards experience, it is particularly changes in the latter that cognitive research has observed. The reconsolidation account described here points toward the potential for therapeutic learning that arises when individuals relate to difficult memories with openness and acceptance and highlights the fact that such learning requires both the activation of relevant memories and the introduction of a new encoding state. Future research and development will have to investigate whether standard mindfulness-based interventions for emotional disorders become more effective if opportunities for exposure to relevant difficult experiences are introduced more systematically. In the context of the prevention of depression, vulnerabilities are latent, and relevant contents may not necessarily reveal themselves or be invited during meditations. It is important, therefore, that teachers skillfully facilitate and encourage exposure and opening. This is particularly relevant in the context of recent adaptations of the program for patients with suicidality and early trauma wherein tendencies toward avoidance are particularly pronounced (Williams, Fennell, Barnhofer, Crane, & Silverton, 2015). In future studies, researchers should test, particularly in these latter contexts, whether increased emphasis on techniques that facilitate these mechanisms will lead to more reliable decreases in cognitive reactivity.

Mindfulness training offers unique potential as a means of increasing awareness for maladaptive responses, teaching patients to respond more skillfully to emotional difficulties, and providing a mental training to foster procedural learning so that trained skills can translate into predispositions toward more adaptive responses, thereby potentially serving to reverse latent vulnerabilities for depression. Neuroimaging research is beginning to provide indicators of vulnerability for depression, and research in expert meditators has brought evidence that consistent training can affect these indicators. More work is needed now to ascertain whether consistent training can bring about similar changes in individuals who are vulnerable for recurrent depression and to use the knowledge gained from these studies to increase effectiveness of interventions. Further development may benefit from systematically using principles of reconsolidation learning so that the potential that lies in an open and acceptant approach to difficult experiences is harnessed more reliably.

Author Contributions

T. Barnhofer drafted the manuscript. T. Barnhofer, J. M. Huntenburg, M. Lifshitz, J. Wild, E. Antonova, and D. S. Margulies contributed to further versions and approved the final manuscript.

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T. Barnhofer is coauthor of a book on mindfulness-based cognitive therapy titled *Mindfulness and the Transformation of Despair* to be published by Guilford Press in August 2015. The remaining authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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