



## Neural effects of mindfulness-based interventions on patients with major depressive disorder: A systematic review

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### ABSTRACT

Growing evidence has suggested that mindfulness-based interventions (MBIs) could have beneficial effects on the acute phase of depression and on the prevention of depressive relapse or recurrence. Despite growing clinical interest, the effects of MBIs on brain functioning in patients with MDD remain unclear. The aim of this systematic review was to assess the changes in brain functioning associated with MBIs in patients with MDD. A systematic search was conducted, and of the 56 articles found, 8 were eligible. MBIs have modulatory effects on several brain regions implicated in the pathophysiology of MDD, such as the prefrontal cortex, the basal ganglia, the anterior and posterior cingulate cortices, and the parietal cortex. These regions have been implicated in self-awareness, attention and emotion regulation. Some of these findings were consistent with the effects of MBIs observed in healthy subjects and patients with other psychiatric disorders, especially enhanced activity in the frontal and subcortical regions related to the improved somatosensory awareness. Further studies are needed to elucidate the mechanisms of MBIs in MDD.

### 1. Introduction

Major depressive disorder (MDD) is among the leading contributors to the global burden of disease (Whiteford et al., 2013), affecting approximately 17% of the population worldwide. This disorder is associated with significant impairments in global functioning and a significant societal economic burden (Kessler et al., 2003). Moreover, depression can be a lethal illness due to its elevated risk of suicide (Trivedi et al., 2006), cerebrovascular disorders, cardiac disease and other medical causes of mortality (Walker et al., 2015). Currently, the first line of treatment for MDD consists of pharmacological approaches using antidepressant medications either associated or not with psychotherapy. However, the current antidepressant treatments are moderately effective, and numerous patients with MDD show partial responses, non-responses or delayed responses to the onset of treatment (Gaynes et al., 2009). Furthermore, even among patients who achieve clinical remission, residual depressive symptoms and relapses are common and often lead to chronic or recurrent MDD (Zajacka et al., 2013). Thus, there is a need to develop innovative therapeutic options or complementary approaches to alleviate symptoms in patients at each

stage of the illness. Among them, in the field of psychotherapy, evidence has suggested that mindfulness-based interventions (MBIs) could collectively be effective as an alternative approach to the acute phase and in the prevention of depressive relapses or recurrences (Gotink et al., 2015).

Among the MBIs elaborated in the past decades, mindfulness-based stress reduction (MBSR; Kabat-Zinn et al., 1985) and mindfulness-based cognitive therapy (MBCT; Segal et al. (2002)) have been repeatedly evaluated in clinical trials of patients with MDD (Gotink et al., 2015). Developed by Kabat-Zinn and colleagues in the 1970s, MBSR has been described as "a group intervention that focuses upon the progressive acquisition of mindful awareness, following these pillars: non-judging, non-striving, acceptance, patience, trust, and non-centering". MBCT was later created by Segal and colleagues as a specific relapse prevention treatment for depression. MBCT is distinguishable from other MBIs due to its focus on depressive symptoms and cognitive processes. This therapy combines psychological, educational components of cognitive behavioral therapy (CBT) for depression, with meditation elements inspired from the MBSR program. A recent meta-analysis of randomized controlled trials using MBSR and MBCT programs in patients with MDD

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demonstrated a significant beneficial effect of MBIs on symptoms of depression ( $d = 0.37$ ;  $p < 0.0001$ ) and anxiety ( $d = 0.49$ ;  $p < 0.0001$ ) in terms of both the acute phase and relapse prevention (Gotink et al., 2015). Specifically, in a randomized, single blind, parallel, controlled trial, MBCT alone was found to be as efficient as pharmacological maintenance therapy in the prevention of depressive relapse (Kuyken et al., 2015). Strikingly, despite the growing clinical interest, the neurobiological mechanisms by which MBCT modulates neural activity in patients with MDD remain unclear. Further investigations of those mechanisms in patients could both provide therapeutic optimization of MBCT and enable a better understanding of MDD pathophysiology. In this context, we decided to conduct a systematic review of controlled studies that evaluated MBCT-induced effects on neural activity in patients with MDD.

## 2. Methods

A systematic review was conducted following the recommendations of the PRISMA guidelines (Liberati et al., 2009).

### 2.1. Eligibility

The inclusion criteria were as follows: i) full-length original articles published in the English language and in peer-reviewed journals; ii) patients with unipolar MDD according to the DSM IV or V diagnosis who were in the acute or remission phase of the illness; iii) use of a clearly described mindfulness procedure; and iv) investigation of neural activity using electroencephalography (EEG), functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), positron emission tomography (PET scan) and/or single-photon emission computed tomography (SPECT). Studies were excluded from the qualitative synthesis in cases of the following: i) insufficient information regarding the MBI procedure; ii) insufficient information regarding the depressive symptoms as assessed by standardized clinical symptom rating scales; and iii) case reports.

### 2.2. Search strategy

We conducted a systematic search of the PubMed and Cochrane Library databases until October 2017 using the following MESH words with no limitation of date: (mindfulness AND depression AND (fMRI OR PET scan OR neuroimaging OR MRI OR MRS OR spectroscopy OR electroencephalography OR EEG)). We also examined the citation lists of the identified publications for additional studies and used the related articles function of the PubMed database for other relevant sources of data. Two investigators (CD and PV) independently screened the title, abstract and key words of each reference identified by the search and applied the inclusion and exclusion criteria. For each potentially eligible reference, the same procedure was applied to the full-text article. Discrepancies between the reviewers were resolved via discussion with a third investigator (JB). The literature search strategy is summarized in Fig. 1.

### 2.3. Data extraction

Two investigators (PV, CD) independently extracted the following data (when available): i) demographic data (number of participants, age, gender, and current treatments), ii) clinical features (diagnosis and symptom severity, as assessed by scores on clinical symptoms rating scales), and iii) characteristics and design of each mindfulness program (program type, session length, session number and frequency).

## 3. Results

### 3.1. Data search process

As shown in Fig. 1, the initial search yielded 56 records after duplicates were excluded. Following preliminary screenings of the titles, key words and abstracts, 26 studies were excluded because they did not contain the necessary data for potential eligibility. Among the 30 studies remaining, 8 fulfilled all the inclusion criteria and were eligible for our study.

### 3.2. Neuroimaging studies investigating mindfulness-induced effects on patients with MDD

The systematic search revealed only one study (Li et al., 2016) that investigated the MBI-induced effects on cerebral plasticity in patients with MDD using neuroimaging techniques. Li et al. (2016) used MRS to investigate the neurochemical effects of MBIs on patients with MDD. After 8 weeks of MBCT, compared with a group of 10 healthy subjects, the group of 16 patients with MDD showed significantly increased levels of N-acetyl-aspartate/total creatine (tCr) in the left anterior cingulate cortex (ACC), and of glutamate/tCr in the left caudate. Conversely, the levels of myoinositol/tCr in the right caudate and of total choline/tCr in the right putamen significantly decreased in patients with MDD after MBI. Interestingly, there was a significant negative correlation between the increase in N-acetyl-aspartate, a marker of neural metabolism and integrity, in the left ACC and a reduction in Hamilton Depression Scale (HAM-D-17) scores. Regarding these findings, the authors suggested that MBIs could normalize the abnormal neurochemical brain activity observed in patients with MDD in frontal and subcortical regions.

### 3.3. EEG studies investigating mindfulness-induced effects on patients with MDD

Our systematic review revealed 7 studies assessing brain activity with EEG after a MBI conducted in patients with MDD (Barnhofer et al., 2007; Keune et al., 2011, 2013; Bostanov et al., 2012; Schoenberg and Speckens, 2014, 2015; Gärtner et al., 2017).

The first EEG study that investigated MBI-induced changes in neural activity was developed by Barnhofer et al. (2007). The authors reported that, while remitted patients receiving usual treatment ( $n = 12$ ) showed significant alterations in frontal alpha asymmetry, patients undergoing an MBCT program ( $n = 10$ ) retained balanced patterns of activation in the frontal cortex at endpoint (Barnhofer et al., 2007). These findings suggested a relapse-prevention effect of MBI on patients with remitted MDD, as it maintained neuronal activity in the left prefrontal cortex.

In 2011, Keune and colleagues failed to replicate these results in a study that included 77 patients with remitted recurrent depression. Despite a beneficial clinical effect of MBCT, the authors observed no difference between the frontal alpha asymmetry of the MBCT group and the waiting list group at endpoint (Keune et al., 2011). In another study, the same group of authors reported a significant shift toward stronger relative right alpha activity, particularly in the mid-frontal region, that occurred simultaneously with the application of mindfulness instruction, relative to resting and negative mood induction measures, in patients with remitted recurrent depression who were receiving a single MBCT session (Keune et al., 2013).

Bostanov et al., 2012 used event-related potentials (ERPs) to measure the effect of MBIs on the late contingent negative variation (LCNV) during either mindfulness instruction or rumination induction conditions, both conducted after a sadness induction task. Here, patients in the remission state of recurrent depressive disorder randomly either received MBCT ( $n = 32$ ) or were placed in a waiting list group ( $n = 32$ ). The authors reported that the LCNV amplitude increased

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