Effects of Mindfulness Training on Emotion Regulation in Patients with Depression: Reduced

Dorsolateral Prefrontal Cortex Activation Indexes Early Beneficial Changes

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The study is registered at ClinicalTrials.gov (NCT02801513; 16/06/2016).

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Abstract

Mindfulness-based interventions (MBI) have been found to be a promising approach for the treatment of recurrent courses of depression. However, little is known about their neural mechanisms. This fMRI study set out to investigate activation changes in fronto-limbic regions during implicit emotion regulation. Depressed patients with a recurrent lifetime history were randomized to receive a two-week MBI ($N=16$ completers) or psycho-education and resting (PER, $N=22$ completers). Before and after, patients underwent fMR imaging while labelling the affect of angry, happy, and neutral facial expressions and completed questionnaires assessing ruminative brooding, the ability to decentre from such thinking, and depressive symptoms. Activation decreased in the right dorsolateral prefrontal cortex (dlPFC) in response to angry faces following MBI, but not following PER. This change was highly correlated with increased decentering, decreased brooding and decreased symptoms. Amygdala activation in response to happy faces decreased following PER, while the MBI group showed a small but insignificant increase. The dlPFC is involved in emotion regulation, namely reappraisal or suppression of negative emotions. Decreased right dlPFC activation might indicate that, following the MBI, patients abstained from engaging in elaboration or suppression of negative affective stimuli; a putatively important mechanism for preventing the escalation of negative mood.

Introduction

Major Depression shows many characteristics of a progressive disease: earlier onsets are associated with poorer outcomes ¹, risk of relapse increases with number of previous episodes ^{2,3}, and there is evidence for functional decline as the disorder accelerates. Recent psychobiological research indicates that recurrent courses are associated with characteristic changes in stress-related physiological and neural functioning ⁴⁻⁶. Over repeated episodes, these changes become increasingly engrained and establish vulnerability mechanisms that can easily take on self-perpetuating dynamics, particularly in patients in whom such dynamics have been instigated at an early age ⁷. Once patients have entered such a course, currently established treatments are less likely to be successful and relapse becomes an increasingly frequent occurrence.

At the core of the cascading processes that drive progression towards increasing persistence are dysregulations in the corticolimbic system that undermine emotion regulation and adaptive stress responding ⁸⁻¹⁰. Patients with depression show hyperactivity of limbic regions involved in generating emotions such as the amygdala and the insula along with ineffective recruitment of cognitive control regions of the prefrontal cortex ^{11,12}. An important indicator of such dysregulations is hyperactivity of the left amygdala, a crucial region for emotion evaluation and generation ¹³. Patients with depression and people at risk for depression display significantly increased left amygdala reactivity to negative affective stimuli ¹⁴⁻¹⁶. Such hyperreactivity increases the likelihood of negative emotional responses to be triggered and may lead into increased persistence of such responses if regulated ineffectively ¹⁷. Findings on cognitive control indicate that, when attempting to regulate negative emotions, patients with depression tend to recruit cognitive control regions of the prefrontal cortex, such as the dorsolateral, ventrolateral and dorsomedial prefrontal cortex areas, more extensively, but less effectively than healthy people ¹⁸⁻²⁰. In line with this, research has found reduced functional connectivity between cognitive control regions and the

left amygdala in depression ^{21,22}. At the same time there is evidence that, in depression, the amygdala and cognitive control regions are more strongly connected to core regions of the default mode network that, among other functions such as autobiographical memory and social working memory ²³, is involved in spontaneous mind wandering ²⁴. Because of this, attempts at cognitive control may easily be undermined and lead into cognitive processes that serve to maintain rather than regulate negative affect. Activity in the dorsolateral prefrontal cortex (dlPFC) has been suggested to play an important role in this context. Under normal circumstances, the dlPFC serves the regulation of negative affect through focussing attention on stimuli that are relevant for reappraisal and keeping reappraisal goals in mind ^{25,26}, or alternatively by facilitating suppression ²⁷⁻²⁹. Yet, increased activity in this region can also lead into maladaptive processes, and has previously been found to be related to self-criticism ³⁰. In patients with depression, hyperactivity of the dlPFC has been observed particularly in the right hemisphere ³¹, which has been suggested to be involved more specifically in the attentional modulation of emotional judgments ³². Increased recruitment of this region might signify an increased attention to negative stimuli that may easily lead into spontaneous self-referential processing, potentially feeding maladaptive ruminative responses that escalate and maintain negative mood states rather than serving effective cognitive control. In line with this, previous research has found the degree of hyperactivity in this region to be correlated with the severity of depression ³¹.

In addition to dysregulations in the processing of negative affective stimuli, there is evidence for reduced processing of positive affective stimuli in depression, which is evident already at early stages of processing. Patients with depression show blunted reactivity of the right amygdala in response to positive affective stimuli ³³. The right amygdala is involved in the detection of relevant social and emotional stimuli, and such blunted reactivity is likely to disrupt encoding of positive experiences ¹³, potentially contributing to a further pathway into persistence of the disorder. There is a need for treatments of depression to address these

pathways, and to build and train emotion-regulatory capacities that counter, and eventually reverse, such dysregulations.

The aim of the current study was to investigate the ways in which training in mindfulness meditation may serve this purpose. Training in mindfulness meditation was originally introduced to the treatment of depression as a means of preventing relapse to depression³⁴⁻³⁶, but has more recently been tested, with promising effects, in the treatment of acute depression, particularly in patients with highly recurrent, chronic and treatment-resistant courses of the disorder³⁷⁻³⁹. More broadly, mindfulness training has been found to represent an effective technique to buffer stress responses⁴⁰. Mindfulness denotes the ability to be aware of present-moment experience with an orientation of acceptance⁴¹. Regular practice helps individuals to build attentional monitoring skills⁴²⁻⁴⁴, while at the same time cultivating an accepting stance towards monitored experience that facilitates adaptive appraisals and decentering^{45,46}, and thereby prevents stress and negative mood from spiralling. In addition, it has been argued that in the treatment of depression, increased awareness of present moment experience with equal attention across the entire range from unpleasant over neutral to pleasant, may counter biases towards reduced encoding of positive experiences and thus address symptoms from the anhedonic spectrum⁴⁷.

By teaching patients to relate to negative experiences from a decentered perspective, mindfulness training may help to reduce extensive attentional engagement, reflected in increases in dorsolateral prefrontal cortex activation, in response to such experiences, and thus reduce tendencies towards ruminative responses that maintain negative mood and depressive symptoms. Furthermore, there is evidence that repeated practice may foster adaptive plasticity in left amygdala reactivity⁴⁸. However, it remains unclear whether such changes can be achieved in patients following only relatively short periods of practice with some recent evidence in healthy people suggesting changes in expert meditators but not following standard mindfulness interventions⁴⁹. Less is currently known about effects of mindfulness practice on

right amygdala reactivity to positive affective stimuli ⁵⁰, although it is plausible to assume that increases in the capacity to become aware of present moment experience are likely to foster increases in reactivity in this region in patients with depression, where reactivity is significantly reduced during acute episodes.

The aim of the current research was to investigate the effects of a brief training in mindfulness (encompassing 28 sessions of formal practice over a period of 14 days) on corticolimbic dysregulations in patients in whom such dysregulations are likely to have become deeply engrained, i.e. those with a recurrent lifetime history of the disorder. For this purpose, we used an incidental emotion regulation task in which patients were asked to label the affect in facial expressions displayed to them. Affect labelling has been shown to act as an implicit form of emotion regulation with effects on emotional outcomes similar to those of more explicit strategies ⁵¹. However, while implicit and often acting without individuals' being aware of its regulatory effects, affect labelling is not effortless as it requires the active transfer of experience into linguistic symbols. In line with this, imaging research suggests that affect labelling downregulates amygdala activation through recruitment of cognitive control regions, namely within the ventrolateral PFC ⁵². This implicit form of emotion regulation is particularly relevant in the context of mindfulness-based interventions given that participants are frequently encouraged to label their experience as part of the practices included in these interventions. Indeed, mindfulness-based interventions emphasise the importance of observing and allowing emotional experiences as an initial response before engaging in any explicit regulation. In line with this, there is evidence to suggest that mindfulness skills can effectively facilitate the effects of affect labelling with research showing dispositional mindfulness to be associated with greater prefrontal cortical activation and reduced amygdala activation during affect labelling ⁵³. Yet, in depression such implicit strategies might become easily derailed by predominant tendencies to engage in elaboration of negative content, reflected in the above described tendencies towards excessive and ineffective dlPFC

activation. Countering such tendencies is thus likely to represent a necessary first step in establishing more adaptive ways of regulating emotion. Mindfulness training aims to build such capacities for attentional modulation particularly in the early stages of interventions. Based on this reasoning, we hypothesized that compared to an active control intervention, mindfulness training would reduce extensive engagement of dlPFC regions in response to negative affective stimuli, and that such reductions would be related to changes in patients' self-reported tendencies to decentre from maladaptive negative thinking, the main psychological mechanism of mindfulness-based interventions in depression ^{35,54–56}. We also investigated whether mindfulness training would reduce left amygdala reactivity to negative affective stimuli and increase right amygdala reactivity to positive affective stimuli.

Method

Design

Participants were randomly allocated, at a ratio of 1:1, to receive either mindfulness training or a control intervention over a period of two weeks, and assessed before and after the intervention.

Participants

Participants had been recruited, by means of advertisements in newspapers, public transport, and on the internet, as part of a larger clinical study ³⁸. Participation in the imaging component was offered as a voluntary extra assessment. Inclusion criteria at initial assessment were a) a current diagnosis of Major Depression as assessed by Structured Clinical Interview for DSM IV ⁵⁷, b) a chronic or recurrent lifetime history of depression, with onset before age 19 and either chronic persistence of symptoms or a history of at least three previous episodes of depression, two of which needed to have occurred during the last two years, c) self-reported severity of current symptoms on a clinical level as indicated by Beck Depression Inventory-II ⁵⁸ scores above 19, d) age 25 to 60 thus excluding cases of late life depression given that such cases might differ in contributing factors, and e) fluency in spoken and written

German. Exclusion criteria were a) history of psychosis or mania, current eating disorder, OCD, current self-harm, current substance abuse or dependence, b) history of traumatic brain injury and c) current treatment with CBT. We allowed patients who were currently taking antidepressants into the study provided that the medication had not been changed during the last four weeks before entry into the study. All participants were right-handed and of Caucasian ethnicity. None of the participants had significant prior experience with meditation or an established regular meditation practice at entry into the study. The flow of participants through the larger trial and the imaging component of the study reported here is depicted in Figure 1. An initial sample of 46 participants volunteered for the imaging assessments and took part in the pre-treatment scan. Two subjects dropped out before the post-treatment scan (both in the mindfulness intervention). Five subjects had to be excluded due to excessive motion during fMRI acquisition (3 in the mindfulness intervention and 2 in the control intervention) and one subject was excluded due to technical issues during scanning (mindfulness intervention). The final sample thus consisted of 38 patients with complete datasets and full adherence (attendance of all three sessions) to the treatments, 16 of whom had been randomized to the mindfulness condition and 22 to the control condition. The two groups did not differ in age, MBI: $M = 43.27$, $SD = 11.64$; PER: $M = 38.67$, $SD = 11.76$; $t(35) = 1.18$, $p = 0.24$, gender distribution, MBI: n (female) = 11 (68.8%); PER: n (female) = 14 (63.6%); $\chi^2(1) = .10$, $p = 0.74$, and education, MBI: n (university degree) = 11 (68.8%); PER: n (university degree) = 11 (50.0%); $\chi^2(1) = 1.33$, $p = 0.25$. The two groups were also comparable in terms of prior episodes of depression, MBI: $Mdn = 6$, $range = [1, 13]$, PER: $Mdn = 7.00$, $range = [3, 35]$, Independent Samples Median Test $p = .90$. Seven of the participants in the MBI group (43.8%) and 12 (54.5%) of the participants in the PER group suffered from a comorbid anxiety or somatoform disorder, $\chi^2(1) = .43$, $p = 0.51$. Of the participants in the MBI group, 6 (37.5) were currently taking antidepressants, 6 (37.5%) had ever taken antidepressants and 13 (81.3%) had ever received psychological therapy. Of the

participants in the PER group, 7 (31.8%) were currently taking antidepressant, 8 (36.4%) had ever taken antidepressants and 21 (95.5%) had ever received psychological therapy, current antidepressants: $\chi^2(1) = .01, p = 0.94$, antidepressants ever: $\chi^2(1) = .13, p = 0.71$, psychological therapy ever: $\chi^2(1) = 1.98, p = 0.16$.

Interventions

The two interventions were delivered in a series of three sessions, two 1.5-hour weekly individual sessions plus a 50-minute follow-up session, and included daily home practice of two sessions of about 25 minutes length. Participants of both groups received a booklet, in which the practices for each day were described in detail along with their rationale and related psycho-educational material. Both interventions followed a manualized approach. During the first session, the therapist introduced the rationale of the respective treatment, clarified in a mutual process whether this rationale was consistent with the experience of the patient, described the most relevant aspects of the treatment in order to familiarize the participant with the approach, and acquainted the participant with the key home practices for the coming week. The second session began with a review of experiences from the first week. The therapist asked for any difficulties that might have arisen with the practices during the previous week and addressed any questions the participants raised. They then introduced the key practices for the second week along with their rationale. The third session served as a follow-up to debrief participants and to help them establish ways of sustaining practices on their own following the end of the study should they wish to do so. This included advise on identifying feasible amounts and patterns of practice.

Participants were free to continue any current medication over the treatment phase under the condition that they would not make changes to their existing regime during this time. All participants agreed not to engage in any other kind of psychological treatment within the duration of the study.

Mindfulness-Based Intervention (MBI). Participants in the meditation training were asked to engage in formal meditation practice for about 25 minutes twice per day on each day of the week using recorded guided meditations. The rationale for the practices was discussed in the therapy sessions and also described in the respective sections of the booklet. Practices were shorter in duration than the practices in standard mindfulness-based interventions, such as Mindfulness-Based Cognitive Therapy (MBCT) ⁵⁹, and did not include prolonged periods of silence (no longer than 3 min). This was in order to allow participants more flexibility in scheduling the practices, and to reduce demands on cognitive resources. However, practices followed a sequence similar to that of MBCT, leading from body scan meditation and mindful movement to sitting meditations focusing on the breath, body sensations, sounds, thoughts, and open awareness, to practices that were more specifically aimed at cultivating openness and acceptance in the face of difficult experiences. Practices during the first week focussed on building attentional capacities and bodily awareness, practices during the second week on using skills to respond more adaptively to negative thoughts and emotions. High frequencies of practice have previously been found to facilitate the development of decentering skills ⁶⁰. Compared to standard MBIs, the sequence of practices in the current intervention also evolved in smaller, more frequent steps, building on each other. In addition to formal meditation practices, participants were asked to engage in informal practices. This included the use of breathing spaces to generalize mindfulness skills to activities in daily life.

Psycho-Education and Resting (PER). The psycho-educational rationale of the control condition was guided by a diathesis-stress model, which depicted depression as a consequence of the interplay between predisposing vulnerability factors and current stress. Psycho-educational components covered information about the signs of depression, and its causes. Participants were educated about the influence of genetic and environmental factors, with a focus on particular stress and its expression in thinking. The programme particularly emphasised the need to balance stress by deliberately taking time to rest. Based on this

rationale, participants were instructed to deliberately and regularly rest and relax, and as best they can to disengage from negative thinking. This strategy was described as an initial and preliminary step towards recovery. In order to formalise this practice, participants were asked to schedule regular rest periods. Length and frequency of these periods mirrored the time demands of the mindfulness meditation training. Participants received audio files with ambient music that they were invited to use should they feel that the music might be helpful in finding rest, relaxation, and distraction from negative thinking. After the first week of the intervention, participants' engagement with the practices was reviewed and participants were guided in building routines to further support their practice.

Participants recorded adherence to the daily practice on protocol sheets over the time of the intervention. The manualised interventions were delivered by trained clinical psychologists, supervised by an expert in MBCT. Assessments of treatment expectancy after the first session of the interventions showed high and comparable ratings for the two intervention, MBI: $M = 8.29$, $SD = 1.13$; PER: $M = 7.42$, $SD = 1.92$ (on a scale from 0 to 10); $t(31) = 1.49$, $p = .14$.

Experimental Paradigm

All included participants underwent MRI scanning before the start of the intervention ('pre') as well as directly after the intervention ('post'). During the fMRI session, participants were asked to label the affect of each of a series of pictures from a standardized set of photographs displaying angry, happy, and neutral facial expressions⁶¹. For each of the conditions, BOLD responses were compared to a fixation cross control condition. The experiment was split into 4 blocks with a 144 second duration each, followed by a 22 second interval of fixation in-between blocks. Within each block, consisting of nine pictures of each affective category, every picture was displayed for 4 seconds and shown only once to avoid repetition and familiarity effects. Fixation crosses were displayed with a variable duration between 2-8 seconds. Participants were instructed to label the facial affect, via button-press,

by choosing from a pair of labels (combinations of ‘angry’, ‘happy’, and ‘neutral’) shown below each target face. Following our previous research, contrasts were calculated with the fixation cross condition. This is contrary to practice in cross-sectional studies on affect labelling that tend to compare against a gender labelling condition. In the current study, we decided against this practice, because a) the longitudinal approach already provides a control condition by comparing against baseline data, b) responses to gender labelling might also change over time and thus introduce confounds, and c) in our previous research subjects reported mentally noting both gender and affect during gender labelling which could potentially introduce bleed-over confounds. Time between scanning sessions did not significantly differ between groups, MBI: $M = 21.1$ days, $SD = 5.57$ days; PER: $M = 21.4$ days, $SD = 5.06$ days; $t(35) = 0.15$, $p = 0.87$).

Interviews and questionnaires

Diagnostic status was assessed using the research Version of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders with the addition of a visual timeline to track lifetime history of the disorder for ratings of chronicity on the Mondimore scale ⁶². All subjects completed the following questionnaires before and after the intervention: Beck Depression Inventory-II (BDI-II) ⁵⁸, Experiences Questionnaire (EQ) ⁶³, and the Ruminative Response Style Questionnaire (RSQ) ⁶⁴.

Beck Depression Inventory-II (BDI-II). Severity of depressive symptoms was measured using the German version of the BDI-II ⁶⁵, a widely used self-report questionnaire. The BDI-II consists of 21 groups of statements that refer to the presence of symptoms of depression. For the purposes of the current study, participants were asked to answer questions with reference to the past week. Internal consistency in the current sample was $\alpha = .74$ at pre-treatment and $\alpha = .89$ at post-treatment.

Experiences Questionnaire – Decentering Scale (EQ Decentering). The EQ Decentering Scale ⁶³ measures decentering “as the ability to observe one’s thoughts and

feelings as temporary, objective events in the mind as opposed to reflections of the self that are necessarily true” (⁶³, p. 234). The EQ was developed based on factor analyses in both healthy and clinical samples. The scale consists of 10 items that are rated on a 5-point Likert scale (1 = never, 5 = all the time). The items, generated by Fresco et al., were designed to cover three facets of decentering, namely the ability to see oneself as not synonymous with one’s thoughts (e.g. “I can separate myself from my thoughts and feelings”), the ability not to habitually react to one’s negative experiences (e. g. “I can observe unpleasant feelings without being drawn into them”), and the capacity for self-compassion (“I am better able to accept myself as I am”). For the current purposes, we had translated the EQ Decentering scale into German. Internal consistency in the current sample was $\alpha = .75$ at pre- and $\alpha = .82$ at post-treatment.

Ruminative Response Scale Questionnaire – Brooding Scale (RRSQ Brooding).

The RRSQ was used to assess different facets of self-reflective thinking. The scale comprises of 22 items, which ask participants to rate on a 4-point scale, ranging from 1 = *never* to 4 = *always*, how much they engage in different cognitive responses when feeling low. The work by Treynor et al. ⁶⁴ has identified subscales for *depression-related rumination* (twelve items, e.g. ‘think about feelings of achiness and fatigue’, ‘think about how hard it is to concentrate’), *brooding* (five items, described as ‘moody pondering’ e.g. ‘think “why can’t I handle things better?”’), and *reflection* (five items referring to neutrally valenced pondering, e.g. ‘analyse recent events to try and understand why you are depressed’). Current analyses focussed on the brooding scale as it indexes detrimental aspects of repetitive negative thinking unconfounded with depressive symptomatology. Internal consistency in the current sample was $\alpha = .78$ at pre-treatment and $\alpha = .82$ at post-treatment.

Procedure

Potential participants were screened over the phone by the recruitment team for the main inclusion and exclusion criteria. Those likely to meet eligibility were invited to an initial

assessment session with blinded assessors to complete the Structured Clinical Interview for DSM-IV ⁵⁷ including lifetime history assessments and the self-report questionnaires. All assessments and therapy sessions took place in the dedicated facilities at the Dahlem Centre for Neuroimaging of Emotions. Assessments were conducted by research assistants blind to treatment allocation. Participants who met inclusion criteria continued this session to fill in self-report questionnaires and then took part in the imaging assessments. Following the pre-treatment assessment, the study manager randomly allocated depressed participants to receive either the mindfulness training or the control training. One week after the end of the two-week intervention period, participants took part in the post-treatment assessment session, which followed the same sequence as the pre-treatment session. After the end of the study, all participants of the control group were offered the opportunity to receive the mindfulness training. The study was conducted over a period of 19 months from September 2013 until March 2015.

Randomization was conducted following a simple randomization protocol using a computer-generated randomization sequence (permuted blocked randomization with blocks of size 4), generated by a researcher outside of the research group, and sealed envelopes that remained concealed until assignment to the groups.

The study protocol for the trial was approved by the ethics committee of the Charité University Medicine Berlin, Campus Mitte (EA4/055/13) and all methods were applied in line with the protocol and relevant regulations. All participants provided written informed consent prior to any research activity.

fMRI data acquisition and analysis

All data were acquired on a 3T Siemens MAGNETOM TRIO scanner (Siemens Medical Solutions, Erlangen, Germany). Structural images covering the whole brain were collected using a T1-weighted MPRAGE sequence, consisting of 170 sagittal slices (1x1x1mm; TI=900ms; TE=2.52ms; TR=1900ms; matrix size=256x256; flip angle=9°).

Functional data were acquired across the whole brain using a T2*-weighted gradient echo planar imaging pulse sequence (37 axial slices; 3mm thickness with 0.3mm gap; voxel size: 3x3x3mm; TR = 2300 ms, TE = 30ms; matrix size=64x64; flip angle = 70°; interleaved acquisition). Task fMRI data was analyzed using SPM12 in conjunction with MATLAB 2013a (The MathWorks, Inc., Massachusetts, US). Preprocessing included the following steps: slice time correction, motion correction, segmentation of high resolution T1-weighted structural images, normalization, and smoothing using an 8mm FWHM Gaussian smoothing kernel. Data quality control comprised visual inspection of raw fMRI time series and T1-weighted scans as well as visual inspection after each preprocessing step. Subjects with translation in excess of 3mm or rotation in excess of 3° in any direction over the course of the scan (i.e. slow but continuous changes) were discarded from further analyses. Additionally, subjects were discarded if the frame-wise displacement (i.e. fast changes from TR to TR) exceeded either 1mm or 1° in any direction (for numbers excluded see the Participants section). In order to reduce movement, tape was placed across the participants' forehead and across the headcoil as a means of providing feedback. First-level time series analysis was performed using general linear models (GLM) in SPM. For each experimental condition (e.g. angry, happy, and neutral faces as well as fixation), the stimulus onsets were convolved with a canonical hemodynamic response function (difference of gamma function) to model the expected BOLD time courses. Additionally, motion parameters and a discrete cosine transform set acting as a high-pass filter (128 s) to remove linear drifts were entered into the regression model as covariates of no interest. Contrasts of interest were based on the comparison of each emotion condition with the fixation condition and subsequently used in a second-level random effects analysis in SPM. Two a-priori regions of interest (ROI) were used to restrict the number of multiple comparisons: (1) a bilateral amygdala mask based on the Harvard-Oxford Atlas, thresholded to 75% probability, and (2) a frontal ROI mask comprising DLPFC, VLPFC, DMPFC, and VMPFC. Based on Wake Forest University's

PickAtlas (WFU PickAtlas; <http://fmri.wfubmc.edu/software/PickAtlas>), this ROI was constructed by combining all Brodman areas, indicated as belonging to the four aforementioned regions according to O'Reilly ⁶⁶.

Statistical analyses of behavioral measures and correlations with brain activation

Repeated-measures ANOVAs (rm-ANOVA) were conducted in SPSS (IBM SPSS, Version 24. Armonk, NY: IBM Corp.) to assess changes in behavioral measures. Associations between brain activation and behavioral measures were assessed using the framework of repeated measures correlation originally introduced by Bland and Altman ^{67,68}. This technique does not violate assumptions of independence of within-subject measurements and typically has greater statistical power over simple regression or correlation methods. Repeated-measures correlation analyses were conducted in R (3.3.1) using the recently released rmcrr package ⁶⁹.

Results

Adherence to home practice

Patients in the mindfulness condition reported a rate of adherence to formal practice of $M = 94.81\%$, $SD = 9.90$, range = [68, 100]. Rate of adherence to rest periods in the control condition was similarly high, $M = 91.87\%$, $SD = 7.12$, range = [75, 100]. There was no significant difference in rate of adherence between the two groups, $t(30) = .97$, $p = .33$. Based on an average length of formal practices of 25 min, over the entire duration of the intervention, participants in the mindfulness intervention practiced for an average of $M = 331.83$ min, $SD = 34.65$, and participants in the control condition practiced for an average of $M = 321.54$ min, $SD = 24.92$.

Behavioral measures

There were no significant baseline differences between intervention groups for any of the questionnaire scores (see Table 1). Analysis of pre-to-post-treatment changes in BDI-II scores yielded a significant main effect of time, $F(1,36) = 48.1$, $p < 0.001$, $\eta^2 = .572$ and a

significant time by intervention interaction, $F(1,36) = 5.9, p = 0.020, \eta^2 = .142$. Both intervention groups displayed significant reductions in symptoms, MBI: $M_{i-j} = -15.72, SE = 2.55, p < .001$; PER: $M_{i-j} = -7.55, SE = 2.18, p = 0.001$. At post-treatment, the MBI group showed significantly lower symptom levels compared to the PER group, $M_{i-j} = -10.08, SE = 2.78, p = 0.001$. These results are in line with effects reported in the larger study including patients who did not take part in imaging assessments ³⁸.

For changes in EQ decentering scores, analysis revealed a significant main effect of time, $F(1,36) = 14.6, p = 0.001, \eta^2 = .288$ and a significant time by intervention interaction, $F(1,36) = 16.0, p < 0.001, \eta^2 = .308$. The MBI group displayed a significant increase in decentering, $M_{i-j} = 5.69, SE = 1.11, p < 0.001$ while no significant changes were observed in the PER group, $M_{i-j} = -0.14, SE = 0.94, p = 0.886$. At post-treatment, the MBI group showed a significantly higher rating of the tendency to ‘decenter’ compared to the PER group, $M_{i-j} = 3.94, SE = 1.62, p = 0.020$.

For RRSQ brooding, analysis revealed a significant main effect of time, $F(1,36) = 4.5, p = 0.041, \eta^2 = .111$ and a significant time by intervention interaction, $F(1,36) = 12.4, p = 0.001, \eta^2 = .256$. The MBI group displayed a significant decrease in RRS brooding scores, MBI: $M_{i-j} = -2.38, SE = 0.64, p = 0.001$ while no significant changes were observed in the PER group: $M_{i-j} = 0.59, SE = 0.55, p = 0.287$. Post-treatment levels of brooding differed significantly between the two intervention groups, $M_{i-j} = -3.40, SE = 1.10, p = 0.004$.

There were no significant harms or unintended effects in either of the groups.

Baseline comparison of brain activation

Comparison of baseline activations between intervention groups yielded no significant differences for any of the emotion conditions in either of the ROI masks.

Pre-post intervention changes in brain activation

Investigation of frontal activation revealed a marginally significant interaction between intervention type and time point in a cluster within right DLPFC for angry faces ($p =$

0.055, voxel-wise FWE-correction, $T > 4.679$; 160 mm³; MNI peak coordinate: 32, 24, 38, see Figure 2). Comparing pre/post activations separately within each group revealed this effect to be mainly driven by a significant decrease in activation in the MBI group ($p = 0.005$, voxel-wise FWE-correction, $T > 3.282$; 56 mm³; MNI peak coordinate: 32, 24, 40, see Figure 2). There were no significant changes in the PER group in any voxels for the angry condition. Investigation of amygdala activation revealed a significant interaction between intervention type and time point in a cluster within the right amygdala for happy faces ($p = 0.001$, FWE-corrected; 136 mm³; MNI peak coordinate: 28, -4, -16, see Figure 3). Comparing pre/post activations separately within each group revealed the interaction effect to be mainly driven by a significant decrease in activation in the control group ($p = 0.002$, FWE-corrected; 392 mm³; MNI peak coordinate: 28, -4, -16, see Figure 3). While the MBI group showed a slight increase in the activation within this cluster from pre to post, this change was not statistically significant. As described further above, these analyses were conducted using a smoothing kernel of 8 mm (FWHM), which was chosen as a default value for reasons of comparability. However, since the amygdala is a small brain structure, it is possible that larger kernel sizes introduce signal variability from surrounding brain structures. In order to exclude the possibility of such influences, we performed a reanalysis of the data smoothed using a 5 mm kernel (FWHM). Results of this analysis were consistent with those using the larger kernel (see Supplement B). In order to test for potential confounding effects of anti-depressant medication on amygdala activation, we compared activation in medicated ($n = 14$) and unmedicated ($n = 24$) patients, irrespective of labelling condition. There were no significant differences in amygdala brain activation in both emotion conditions, happy and angry faces, neither at baseline nor after the intervention ($p < 0.001$, uncorrected). For exploratory whole brain analyses of angry as well as happy faces see Supplement A Figures 1-10.

Correlations between brain activation changes and changes in behavioral measures

Repeated-measures correlations analyses revealed significant correlations between changes in brain activation and changes in behavioral measures (see Tables 2 and 3). Specifically, activation in the frontal cluster (right dlPFC) revealing a significant pre-to post decrease in response to angry faces in the MBI group was significantly correlated with changes in EQ Decentering, RRSQ Brooding, and change in BDI-II scores (see Figure 4). There were no significant correlations between brain activation and any of the questionnaires' subscales in the control group. Exploration of indirect effects yielded no evidence for a mediational role of changes in decentering or any of the other psychological variables in conferring the differential effect of treatment on changes in activation in the right dlPFC clusters. However, it is important to note in this context that sample size was insufficient to test such effects reliably. For the amygdala cluster that displayed a significant pre-to-post activation decrease in response to happy faces in the control group, there was no significant correlation with any of the questionnaire measures. For the MBI group there were no significant correlations with EQ Decentering, RRSQ Brooding and BDI-II scores.

Discussion

In line with our hypotheses, our data provide evidence that mindfulness training may change the ways in which patients process negative affective stimuli, represented here by angry faces. Participants in the MBI group showed significant reductions in right dlPFC activity from before to after the brief training. The dlPFC is involved in emotion regulation through maintaining attention on affective stimuli in support of reappraisal and suppression processes^{25–28}. Previous research has indicated that depression is associated with more extensive, but less efficient recruitment of this area during emotion regulation^{18–20}. While it remained untested in our study whether our sample did indeed show such dlPFC deficits at baseline, the current findings point towards the possibility that mindfulness training may foster more effective emotion-regulation in depression by countering characteristic tendencies towards excessive or ineffective dlPFC engagement. This observation is in line with recent imaging research in healthy participants indicating that trait mindfulness is associated with reduced recruitment of cognitive control regions during regulation of negative emotions⁷⁰.

The lateralization of the observed effect is consistent with previous reports that have suggested increased dlPFC activation in depression to be particularly pronounced in the right hemisphere³¹, which in terms of its function has been suggested to be specifically involved in the attentional modulation of emotional judgments³². With mindfulness practice, patients are trained to let go of the attempt to downregulate or suppress negative emotions, but to simply experience them as they arise and pass, that is to observe them from a decentered perspective^{34–36}. Diminished dlPFC activation in response to negative affective stimuli in depression might therefore be indicative of the abstinence of extensive appraisal or suppression strategies that could, directly or paradoxically, lead into maladaptive elaborative processes. In line with this view, we found changes in dlPFC activation in response to negative affective stimuli to be strongly associated with the degree to which patients reported increases in the ability to decentre from negative thinking, decreases in their tendencies towards ruminative brooding,

and decreases in levels of current symptoms. Indeed, exploration of individual data indicated that these relations were highly consistent across the entire sample of those who received the MBI. These findings suggest that reduced dlPFC activation in response to negative affective stimuli may represent an important neural signature of the mechanisms conveying effects of mindfulness in the treatment of depression, potentially reflecting reduced attentional engagement in such stimuli, and point towards the importance of these mechanisms particularly at early stages of therapy in acutely depressed patients with chronic and recurrent histories of depression. While these findings point towards the potential of mindfulness practice to counter characteristic deficits in depressed patients, it is worth noting in this context that studies in healthy, stressed, and anxious samples have tended to find increased rather than decreased activity in prefrontal cortex regions following standard mindfulness-based interventions ⁷¹. It will be interesting therefore to further explore how effects of the training might express itself in patients with depression in the context of tasks that do not involve the regulation of responses to affective stimuli.

While the current findings indicate changes in regulatory neural signatures, we did not find evidence for significant reductions in left amygdala reactivity to negative affective stimuli following mindfulness training. Increased amygdala reactivity to negative affective stimuli is likely to arise as part of a highly conservable brain adaptation to continuing stress and may thus more easily develop into a stable vulnerability for the disorder ⁷². At the same time, patients with emotional disorders might find it more difficult to recruit adaptive emotion regulation strategies. Indeed, a study in patients with social anxiety and depression has found that affect labelling led to upregulation rather than downregulation of amygdala activation ⁷³. It is possible, therefore, that reversal of increased amygdala reactivity may require more extensive mindfulness practice. In line with this, recent research has reported relations between amount of practice and reductions in left amygdala reactivity in expert meditators

while there were no effects of a standard mindfulness intervention on left amygdala reactivity to negative affective stimuli ⁴⁹.

In contrast to the findings regarding responses to negative affective stimuli, our results provided some evidence for relevant changes in amygdala activation in response to positive affective stimuli. Data analysis of brain activation within the predefined amygdala region of interest revealed a significant interaction in response to the happy faces, which was due to small but insignificant increase in activation in the MBI group, while participants of the control condition showed a significant reduction of amygdala activation from before to after the intervention. The small increase in the MBI group was negatively correlated with symptom change, indicating that increased amygdala activation in response to positive stimuli went along with symptom reduction. While the participants in the PER control condition thus seem to have habituated to positive affective stimuli, participants in the MBI condition maintained or slightly increased their sensitivity. The fact that trends for changes in brain activation became visible in response to positive affective stimuli, but not negative affective stimuli, is in line with previous research suggesting that increased amygdala reactivity to negative affective stimuli represents a more persistent feature, while reductions in amygdala reactivity to positive affective stimuli seem to be more dynamically associated with the state of depression ⁶⁷. It seems plausible therefore that changes in reactivity to positive affective stimuli would start to occur after relatively brief training in mindfulness. While we did not observe significant increases in reactivity to positive stimuli in the MBI group, the pattern of findings observed seems to be in line with a growing body of research showing that mindfulness training may not only serve to buffer responses to stress but can also help to foster dynamics of positive affect ⁴⁷.

Our findings have to be interpreted in light of a number of limitations. The study is based on a relatively small sample and therefore requires replication. In particular, research including larger groups of patients is necessary in order to formally test whether the changes

observed in our study actually mediate treatment outcomes. Furthermore, we did not calculate contrasts of affect labelling with another labelling condition such as gender labelling, and it is therefore not possible to attribute activation patterns specifically to affect labelling as compared to other forms of labelling. Instead it is possible that the patterns observed may apply more generally to the processing of emotional faces. Comparisons with previous research will have to take into account that the current findings relate to the effects of an intervention that was substantially shorter in duration than standard mindfulness-based interventions. However, within the intervention period of two weeks, practice intensity was similar in terms of practice time per day while practices were shorter and more frequent than in standard mindfulness interventions. Furthermore, the intervention placed strong emphasis on motivating patients to practice and levels of adherence – on average participants reported to have engaged in more than 90 per cent of formal practices - were significantly higher than commonly seen with standard interventions ⁷⁴. The current study thus offers insights into the effects of relatively focused practice over a brief period of time. The efficacy of this approach is reflected in the significant reductions in symptoms observed following mindfulness training in a group that would commonly be considered as treatment-resistant (for a report of symptom changes in the larger sample including those who did not take part in the imaging component reported here, see ³⁸).

By investigating the effects of a brief intervention, the current study aimed to provide an initial step in understanding the neural mechanisms of mindfulness training in the treatment of depression. Our findings suggest that while brief training in mindfulness does not lead to reductions in amygdala reactivity to negative affective stimuli, early effects of the training become visible in reduced recruitment of dlPFC. Given our correlative findings, this effect seems to reflect changes in attentional modulation that reduce the likelihood of patients to be drawn into dominant maladaptive responses that would otherwise lead to escalation of negative emotions, a change that corresponds with the aims of early stages of mindfulness

training. At the same time, brief mindfulness practice may support patients in increasing responsivity to positive affective stimuli, indicating the potential of mindfulness practices for supporting the encoding of positive experiences and thus countering characteristic anhedonic biases in depression. Further research will have to test in how far more extended training may translate into changes in left amygdala reactivity to negative affective stimuli and eventually alter the structural changes underlying increased reactivity in patients with chronic and recurrent histories of depression ⁷⁵.

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Acknowledgments

We thank our participants for giving time to take part in this study. This research was funded by German Research Foundation Grant BA2255 3-1 awarded to TB and a Francisco J. Varela award from the European Mind and Life Institute to BKH, who also gratefully acknowledges a private donation by Tussi Maria Kluge. TB was supported in conducting this research by a Heisenberg Fellowship from the German Research Foundation (BA2255 2-1). The funders had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article.

Author Contributions

TB, TJR, and BKH wrote the main manuscript text, TJR conducted fMRI imaging analyses and prepared figures 1 to 3, all authors reviewed the manuscript and approved of the final version; TB and BKH designed the experiment; EW, MF, MG, JMH and TAS conducted the assessments and helped with data processing; SG, MG, YF, and MB, advised on the design of the study, implementation of tasks, and the processing and analysis of fMRI data; MB advised on the design of the study and facilitated recruitment of patients.

Competing Interests Statement

Thorsten Barnhofer and Britta K. Hölzel are authors of books on mindfulness-based interventions and have received honoraria for workshops on mindfulness. All other authors declare no conflicts of interest.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Figure Legends

Figure 1. Flow of participants through the study.

Figure 2. Brain activation in response to angry faces decreases in the right DLPFC following MBI. Left: cluster in right DLPFC displaying a trend significant interaction effect (intervention group $\times$ time point). Bar plot of mean beta estimates plotted according to intervention group / time point, averaged over all voxels revealing the trend significant interaction effect. Right: cluster in right DLPFC displaying a significant decrease in activation in the MBI group. Bar plot of mean beta estimates plotted for the difference between time points (TP2-TP1) according to intervention group. * = $p < 0.05$, FWE-corrected

Figure 3. Brain activation in response to happy faces decreases in the PER, but not the MBI group. Left: cluster in right amygdala displaying a significant interaction effect (intervention group $\times$ time point). Bar plot of mean beta estimates plotted according to intervention group / time point, averaged over all voxels revealing the significant interaction effect. Right: cluster in right amygdala displaying a significant decrease in activation in the PER group. Bar plot of mean beta estimates plotted for the difference between time points (TP2-TP1) according to intervention group. * = $p < 0.05$, FWE-corrected

Figure 4. Relationship between brain activation changes in DLPFC in response to angry faces and changes in clinical characteristics. Pairs of dots connected by a line represent participants. Black dots indicate values for time point 1, gray dots indicate values for time point 2. Top row: association of brain activation and BDI-II, RSSQ brooding, and EQ decentering in the MBI group. Bottom row: association of brain activation and BDI-II, RSSQ Brooding, and EQ Decentering in the PER group. BDI-II = Beck Depression Inventory II, RSSQ Brooding =

Ruminative Response Scale – Brooding Subscale, EQ-Decentering: Experiences

Questionnaire – Decentering Subscale.

Table 1

Means and Standard Deviations of Symptom and Cognitive Vulnerability/Resilience Measures at Pre- and Post-Assessment in the MBI Group and the PER Group

	MBI		PER	
	Pre	Post	Pre	Post
BDI-II	27.0 (6.24)	11.3 (5.75)	28.9 (6.65)	21.4 (9.95)
EQ-Decentering	23.9 (6.18)	29.6 (5.27)	25.8 (4.25)	25.7 (4.66)
RRSQ-Brooding	12.1 (3.36)	9.7 (2.60)	12.5 (3.56)	13.1 (3.79)

Note. BDI-II = Beck Depression Inventory II, EQ = Experiences Questionnaire – Decentering Subscale; RRSQ-Brooding= Ruminative Response Style Questionnaire – Brooding Subscale

Table 2

Correlations between Brain Activation Changes in Response to Angry Faces and Questionnaire Scores, Extracted for the Significant Right DLPFC Cluster in the MBI Group (Upper Panel) and the PER Group (Lower Panel)

MBI	<i>r</i>	<i>df</i>	<i>p</i>	95% <i>CI</i>
EQ-Decentering	-.52	15	.033	[-.81, -.01]
RRSQ-Brooding	.60	15	.010	[.13, .85]
BDI-II	.82	15	.005	[.54, .94]

PER	<i>r</i>	<i>df</i>	<i>p</i>	95% <i>CI</i>
EQ-Decentering	-.13	21	.532	[-.53, .31]
RRSQ-Brooding	.29	21	.170	[-.15, .64]
BDI-II	-.20	21	.360	[-.58, .25]

Note. BDI-II = Beck Depression Inventory II, EQ = Experiences Questionnaire – Decentering Subscale; RRSQ-Brooding= Ruminative Response Style Questionnaire – Brooding Subscale

Table 3

Correlations between Brain Activation Changes during Happy Faces and Questionnaire Scores, Extracted for Right Amygdala in the MBI Group (Upper Panel) and the PER Group (Lower Panel)

MBI	<i>r</i>	<i>df</i>	<i>p</i>	95% <i>CI</i>
EQ-Decentering	.45	15	.064	[-.07, .78]
RRSQ-Brooding	-.45	15	.066	[-.78, .07]
BDI-II	-.47	15	.056	[-.79, .05]

PER	<i>r</i>	<i>df</i>	<i>p</i>	95% <i>CI</i>
EQ-Decentering	-.37	21	.076	[-.69, .06]
RRSQ-Brooding	-.04	21	.856	[-.46, .39]
BDI-II	.37	21	.082	[-.07, .69]

Note. BDI-II = Beck Depression Inventory II, EQ = Experiences Questionnaire – Decentering Subscale; RRSQ-Brooding= Ruminative Response Style Questionnaire – Brooding Subscale

Figure 1.

Figure 2.

Figure 3.

Figure 4.