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## Mindfulness-Based Therapy Regulates Brain Connectivity in Major Depression

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### Keywords

Major depression · Mindfulness-based therapy · Nonpharmacological intervention · Functional connectivity · Frontoparietal network

Dear Editor,

Major depressive disorder (MDD) is associated with abnormal functional interactions among large-scale brain networks [1]. The development of more comprehensive neural models of MDD promises to inform treatment by targeting the modulation of specific brain circuits. Here, we report findings from a randomized, active-controlled trial examining whether mindfulness-based therapy – a clinically effective nonpharmacological treatment for depression – can regulate specific patterns of functional brain connectivity in clinically depressed patients.

Mindfulness-based therapy is rapidly gaining popularity as an evidence-based treatment for depression [2]. What distinguishes mindfulness-based therapies from other psychological interventions is their emphasis on meditative training designed to promote attention, interoceptive awareness, and self-regulation. Prior research investigating healthy populations has demonstrated that

meditation training can induce functional and structural plasticity within key nodes of the frontoparietal, default, and salience networks [3, 4] – brain circuits centrally implicated in the pathophysiology of MDD [1]. However, despite promising clinical data from well-controlled trials [2], the neural mechanisms of mindfulness in the treatment of depression remain unknown.

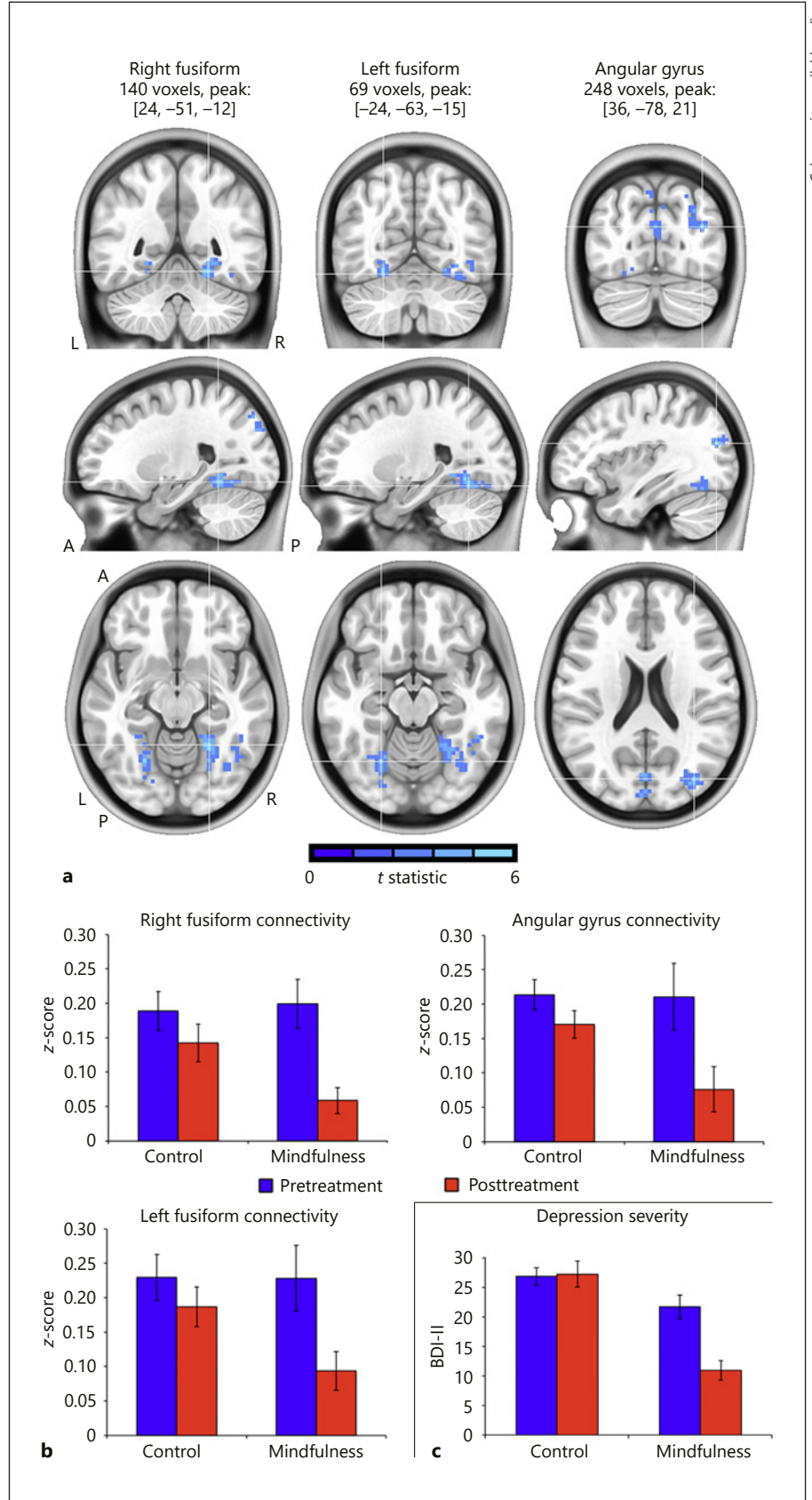
For the first time, this study used fMRI to examine the impact of mindfulness-based therapy on brain function in MDD. Specifically, we investigated the effects of a brief mindfulness-based intervention on resting-state functional connectivity in individuals with recurrent MDD. Patients were randomized to either a 2-week mindfulness-based therapy (consisting of three individual face-to-face sessions and daily guided home practice) or a relaxation-based control intervention. The control condition mirrored the mindfulness intervention in terms of practice structure and time commitment, allowing us to specify the impact of meditative training beyond nonspecific factors such as provision of a rationale, therapist contact, and quiet rest. Before and after treatment, resting-state fMRI data were acquired. Data from 31 participants were suitable for analysis.

At the behavioural level, mindfulness-based therapy led to significant decreases in depressive symptoms (as measured by the Beck Depression Inventory-II) relative to the control intervention (Fig. 1c). In terms of brain changes, networks of interest were identified a priori based on the meditation and MDD neuroimaging literatures. Functional connectivity was quantified using a standard seed-based approach. We placed 10-mm seeds centred on each of the bilateral dorsolateral prefrontal cortices (DLPFC), bilateral anterior insula (aINS), and bilateral posterior cingulate cortex (PCC) for the frontoparietal, salience, and default networks, respectively. Next, we implemented a spreading interaction approach (as in [5]) to specifically identify voxels in which the mindfulness group exhibited change from pre- to post-treatment while the control group did not.

As displayed in Figure 1a, whole-brain analyses yielded three statistically significant clusters related to the DLPFC seed: bilateral fusiform gyrus (right: 140 voxels, peak voxel MNI coordinates [24, -51, -12]; left: 69 voxels [-24, -63, -15]) and right angular gyrus (248 voxels [36, -78, 21]). The significant spreading interactions were driven by decreases in DLPFC connectivity from pre- to post-treatment in the mindfulness group while the control group signal did not change (Fig. 1b). Whole-brain analyses related to the aINS and PCC seeds did not yield statistically significant results. It is important to note that we had a small sample size and so our findings should be interpreted with due caution pending replication.

These results show that mindfulness-based therapy for MDD ameliorates clinical symptoms while regulating resting-state functional connectivity, over and above the effects of a relaxation-based

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**Fig. 1.** Changes in resting-state functional connectivity associated with mindfulness-based therapy for major depression. **a** Seed-based spreading interaction analysis revealed decreases in resting-state functional connectivity between the DLPFC seed and three clusters (bilateral fusiform gyrus and right angular gyrus) from pre- to post-treatment in the mindfulness-based therapy group but not in the relaxation control group (whole brain-corrected,  $p < 0.05$ ). Crosshairs mark peak voxels in bilateral fusiform gyrus (right: 140 voxels, MNI coordinates [x, y, z (mm): 24, -51, -12]; left: 69 voxels [-24, -63, -15]), and right angular gyrus (248 voxels [36, -78, 21]). Note that multiple statistically significant clusters may be viewable in any given single slice image. **b** Mean functional connectivity (z-scores) from each of the significant clusters identified in the seed-based analysis, plotted by group and time. **c** Mindfulness-based therapy led to better clinical outcomes than did the control intervention. ANCOVA revealed that post-treatment self-report depression scores (Beck Depression Inventory-II, BDI-II) were significantly lower in the mindfulness-based therapy group ( $n = 14$ ) compared to the relaxation control group ( $n = 17$ ), after controlling for pretreatment BDI-II scores ( $F(1, 28) = 22.83, p < 0.001, \eta^2 = 0.45$ ).

control intervention. We found that 2 weeks of mindfulness-based therapy reduced connectivity between the frontoparietal control network (DLPFC) and regions involved in higher-order processing of sensory input (bilateral fusiform gyrus and right angular gyrus, which spanned the visual, frontoparietal, and dorsal-attention networks). Our results extend previous findings showing that psychological treatments for MDD can modulate functional connectivity in relevant brain networks [6]. However, whereas prior studies lacked a control treatment group, our study is the first active-controlled report to demonstrate that a psychological intervention exerts a specific influence on brain connectivity in MDD.

We found that mindfulness-based therapy reduced connectivity between the DLPFC seed and bilateral fusiform gyrus. As part of the ventral visual stream in the canonical visual network, the fusiform gyrus plays an important role in higher-order processing of incoming visual information, including social and emotional cues [7]. The present finding aligns with the results of a prior study of long-term meditators, which similarly showed decreased resting-state functional connectivity between the DLPFC and regions of the visual network (including cuneus and occipital gyrus) [8]. The fusiform gyrus in particular has been implicated in studies of meditation [3, 4] as well as clinical depression and antidepressant drug action [9].

The mindfulness-based intervention also reduced connectivity between the DLPFC seed and a cluster in the right angular gyrus. This cluster was centred in the canonical visual network and spanned into the frontoparietal and dorsal-attention networks. Meta-analytic findings link MDD to dampened connectivity both within and between the frontoparietal and dorsal-attention networks [1]; thus, contrary to our findings, we might have expected the mindfulness treatment to increase connectivity between the DLPFC and this angular gyrus cluster. On the other hand, at least four studies have reported increased connectivity between frontoparietal network regions in patients with MDD [1]. Moreover, an investigation of successful electroconvulsive therapy for severe MDD revealed substantial decreases in frontoparietal network connectivity [10]. That study was the only other investigation of MDD treatment, besides the present report, to show changes in connectivity between regions of the frontoparietal network; thus, it is noteworthy that connectivity of this network was reduced as a result of intervention, as is consistent with our current findings.

In conclusion, the present report elucidates the impact of mindfulness-based therapy on functional brain organization in major depression. We show, using a randomized active-controlled design, that a brief, clinically effective mindfulness intervention functionally decouples top-down control regions from brain areas implicated in sensory, affective, and attentional processing. While previous work has demonstrated the clinical impact of mindfulness training, the present findings shed light on the precise neural targets, providing new insight into the specificity of this therapeutic approach.

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#### Statement of Ethics

The study protocol was approved by the ethics committee of the Charité University Medicine Berlin, Campus Mitte (EA4/037/11). All participants provided written informed consent.

#### Disclosure Statement

The authors have no conflicts of interest to declare.

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