Psychotherapy and Psychosomatics

Received: April 9, 2019
Accepted after revision: May 26, 2019
Published online: September 11, 2019

Psychother Psychosom 2019;88:375–377
DOI: 10.1159/000501170

Mindfulness-Based Therapy Regulates Brain Connectivity in Major Depression

Michael Lifshitz[a, b] *Matthew D. Sacchet*[c] *Julia M. Huntenburg*[d, e] *Thomas Thiery*[f] *Yan Fan*[g, h] *Matti Gärtner*[h] *Simone Grimm*[h] *Emilia Winnebeck*[h, i] *Maria Fissler*[h, i] *Titus A. Schroeter*[i] *Daniel S. Margulies*[j] *Thorsten Barnhofer*[k]

[a]Integrated Program in Neuroscience, McGill University, Montreal, QC, Canada; [b]Department of Anthropology, Stanford University, Stanford, CA, USA; [c]Center for Depression, Anxiety, and Stress Research, McLean Hospital, Harvard Medical School, Belmont, MA, USA; [d]Max Planck Research Group for Neuroanatomy & Connectivity, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; [e]Neurocomputation and Neuroimaging Unit, Department of Education and Psychology, Free University of Berlin, Berlin, Germany; [f]Department of Psychology, Université de Montréal, Montreal, QC, Canada; [g]Department of Psychology and Neurosciences, Leibniz Research Centre for Working Environment and Human Factors, Dortmund, Germany; [h]Clinic for Psychiatry and Psychotherapy, Charité University Medicine Berlin, Berlin, Germany; [i]Dahlem Institute for Neuroimaging of Emotion, Freie Universität, Berlin, Germany; [j]Centre National de la Recherche Scientifique (CNRS) UMR 7225, Frontlab, Institut du Cerveau et de la Moelle Épinière, Paris, France; [k]School of Psychology, University of Surrey, Guildford, UK

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

Michael Lifshitz and Matthew D. Sacchet contributed equally to this work as lead authors. Daniel S. Margulies and Thorsten Barnhofer contributed equally as senior authors.

E-Mail karger@karger.com
www.karger.com/pps

Michael Lifshitz
Department of Anthropology, Stanford University
Building 50, 450 Serra Mall
Stanford, CA 94305 (USA)
E-Mail lifshitz@stanford.edu

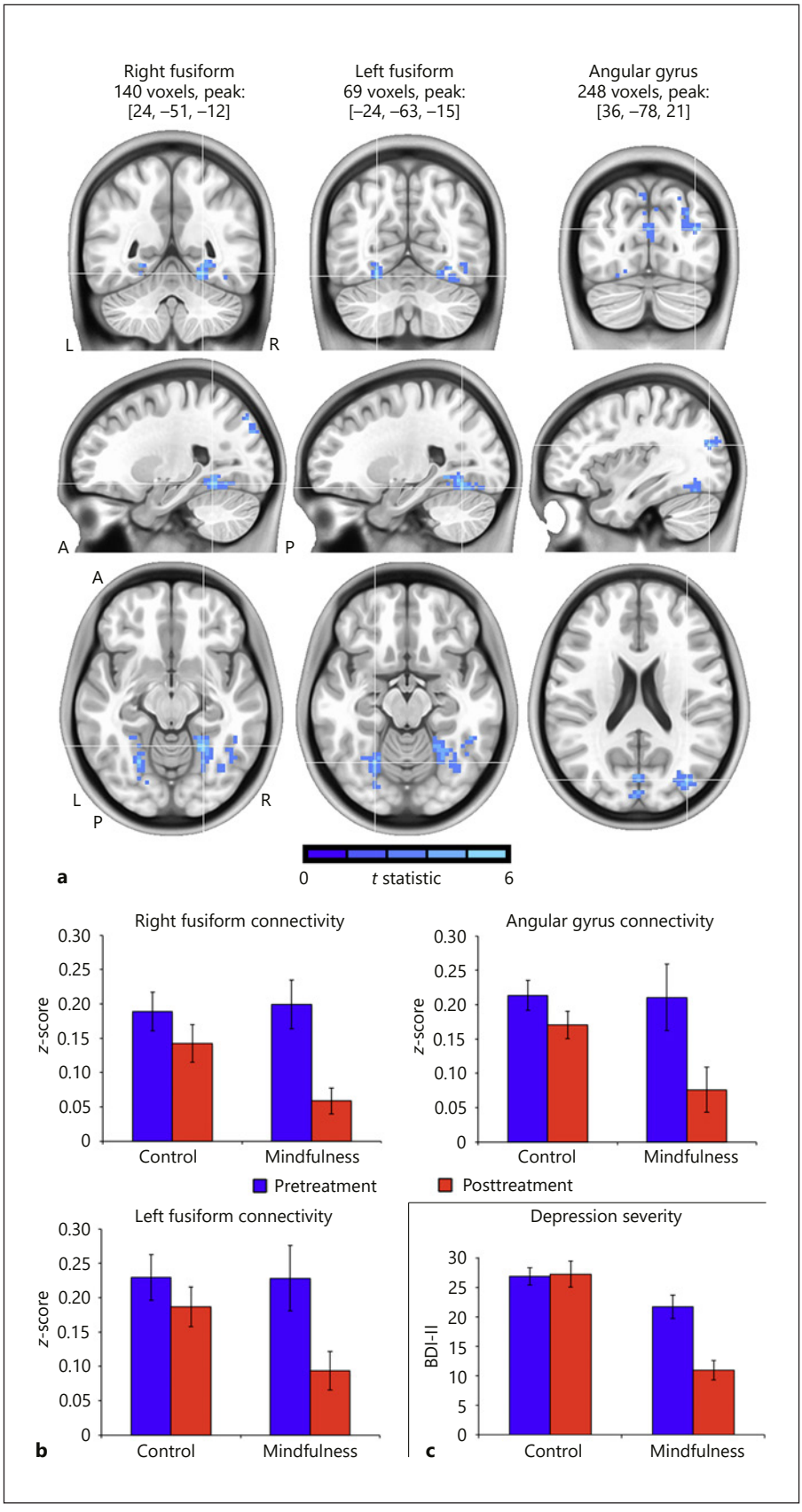

Fig. 1. Changes in resting-state functional connectivity associated with mindfulness-based therapy for major depression. **a** Seed-based spreading interaction analysis revealed decreases in resting-state functional connectivity between the DLPFC seed and three clusters (bilateral fusiform gyrus and 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.

Acknowledgment

We thank our study participants for their time and effort. In addition, we are grateful to Ishan Walpola for helpful suggestions throughout the preparation of the manuscript. The study is registered at ClinicalTrials.gov (NCT02801513).

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.

Funding Sources

Michael Lifshitz acknowledges a Francisco J. Varela Research Award from the Mind and Life Institute and a Vanier Graduate Scholarship from the Natural Sciences and Engineering Research Council of Canada. Thorsten Barnhofer acknowledges support by a Heisenberg Fellowship from the German Research Foundation (BA2255 2-1). This research was funded by German Research Foundation (Deutsche Forschungsgemeinschaft) Grant BA2255 3-1, awarded to Thorsten Barnhofer. The funders had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article.

References

1 Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. JAMA Psychiatry. 2015 Jun;72(6):603–11.
2 Goldberg SB, Tucker RP, Greene PA, Davidson RJ, Wampold BE, Kearney DJ, et al. Mindfulness-based interventions for psychiatric disorders: A systematic review and meta-analysis. Clin Psychol Rev. 2018 Feb;59:52–60.
3 Fox KC, Dixon ML, Nijeboer S, Girn M, Floman JL, Lifshitz M, et al. Functional neuroanatomy of meditation: A review and meta-analysis of 78 functional neuroimaging investigations. Neurosci Biobehav Rev. 2016 Jun;65:208–28.
4 Fox KC, Nijeboer S, Dixon ML, Floman JL, Ellamil M, Rumak SP, et al. Is meditation associated with altered brain structure? A systematic review and meta-analysis of morphometric neuroimaging in meditation practitioners. Neurosci Biobehav Rev. 2014 Jun;43:48–73.
5 Creswell JD, Taren AA, Lindsay EK, Greco CM, Gianaros PJ, Fairgrieve A, et al. Alterations in resting-state functional connectivity link mindfulness meditation with reduced interleukin-6: A randomized controlled trial. Biol Psychiatry. 2016 Jul;80(1):53–61.
6 Shou H, Yang Z, Satterthwaite TD, Cook PA, Bruce SE, Shinohara RT, et al. Cognitive behavioral therapy increases amygdala connectivity with the cognitive control network in both MDD and PTSD. Neuroimage Clin. 2017 Jan;14:464–70.
7 Schilbach L, Bzdok D, Timmermans B, Fox PT, Laird AR, Vogeley K, et al. Introspective minds: Using ALE meta-analyses to study commonalities in the neural correlates of emotional processing, social & unconstrained cognition. PLoS One. 2012;7(2):e30920.
8 Hasenkamp W, Barsalou LW. Effects of meditation experience on functional connectivity of distributed brain networks. Front Hum Neurosci. 2012 Mar;6:38.
9 Ma Y. Neuropsychological mechanism underlying antidepressant effect: A systematic meta-analysis. Mol Psychiatry. 2015 Mar;20(3):311–9.
10 Perrin JS, Merz S, Bennett DM, Currie J, Steele DJ, Reid IC, et al. Electroconvulsive therapy reduces frontal cortical connectivity in severe depressive disorder. Proc Natl Acad Sci USA. 2012 Apr;109(14):5464–8.