Mindfulness training changes brain dynamics during depressive rumination: A randomized controlled trial.

Anne Maj van der Velden*[12], Jacqueline Scholl*[3], Else-Marie Elmholt[45], Lone Fjorback[2], Catherine Harmer[2], Sara Lazar[6], Mia O'Toole[4], Jonathan Smallwood[7], Andreas Roepstorff**[28], Willem Kuyken**[2]

[1] Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
[2] Department of Psychiatry, Oxford University, Oxford, United Kingdom
[3] Department of Experimental Psychology, Oxford University, Oxford, United Kingdom
[4] School of Business and Social Sciences, Aarhus University, Aarhus, Denmark
[5] NIDO, Regional Hospital West Jutland, Herning, Denmark
[6] Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
[7] Department of Psychology, University of York, York, United Kingdom
[8]School of Culture and Society, Aarhus University, Aarhus, Denmark

*shared first authorship ** shared senior authorship

ABSTRACT

Mindfulness meditation trains adaptive attention regulation and present moment embodied awareness, skills that may be particularly useful during depressive mind states characterized by negative ruminative thoughts. We investigated the neurocognitive mechanisms of Mindfulness-Based Cognitive Therapy (MBCT) treatment of recurrent depression across three states (rest, mindfulness, rumination) in a randomized controlled design. We found that MBCT led to reduced depressive symptoms, increased ability to sustain and control attention to body sensations, and decreased connectivity between the salience network and visual brain areas (occipital cortex and lingual gyrus) during a rumination state. Change in salience network connectivity was mediated by the ability to sustain and control attention to body sensations, suggesting that salience network plasticity during depressive rumination is related to embodied attention regulation capacity. These concurrent neural and psychological changes may be a mechanism by which MBCT works to increase resilience and reduce vulnerability to relapse.

INTRODUCTION

Depression is a leading cause of disability worldwide and highly recurrent (World Health Organization, 2020). Risk of relapse increases for every episode of depression, and after 3 episodes the relapse rate can be as high as 80%, and many individuals do not fully recover (Richards, 2011; Kupfer et al 1992). Recurrent depression is characterized by increased cognitive reactivity, in which changes in mood can easily activate negative biases and ruminative states, reminiscent of previous episodes. Such ruminative states have been linked to the onset, maintenance and perpetuation of depressive symptoms and the risk of relapse (Buckman et al., 2018; Figueroa et al., 2015; Segal, Williams., & Teasdale, 2013; Segal et al., 2006).

Mindfulness-Based Cognitive Therapy (MBCT) is an effective treatment for prevention of relapse risk amongst individuals with a history of recurrent depression (Kuyken et al., 2016) and is recommended as a preventative treatment in a number of national health guidelines such as the National Institute for Health (e.g. NICE, 2018). MBCT trains adaptive attention regulation and present moment embodied awareness, and teach individuals with recurrent depression tools to recognize and decouple from conditioned patterns of ruminative negative thought by shifting the attentional focus to the body. This mode of present-moment sensory awareness is believed to be incompatible with a ruminative mode of focused attention on the symptoms of one's distress, and on its possible causes and consequences. Furthermore by shifting attention to the body, ruminative thought processes are more easily seen for what they are: overly negative predictions based on past experience rather than an objective reality. Such adaptive attention regulation is hypothesized to be a core skill by which MBCT is effective in preventing depressive relapse (Segal et al., 2006).

Current research on the mechanisms by which MBCT treatment reduces depressive symptoms and relapse risk has focused mainly on self-reported psychological traits and there is a lack of experimental research on how MBCT impact neurocognitive and psychological processes during ruminative mind states, where risk of relapse is high (van der Velden et al., 2015). (Hence, in this study we investigated the neurocognitive mechanisms and concurrent psychological processes using a randomized controlled design tailored to address how MBCT can affect general vulnerability (resting state), a mindfulness meditation state (proposed mechanism), and a state in which cognitive vulnerability to relapse was induced (rumination).

A network-based functional connectivity approach holds great promise in understanding dynamic and complex states of mind. In particular, two networks have received much attention in the context of the clinical neuroscience of depression and been linked to depression vulnerability, rumination, and treatment response: the salience network (SN) and the default mode network (Dichter, Gibbs, & Smoski, 2015; Fox et al., 2014; Godlewska et al., 2018; Hamilton, Farmer, Fogelman, & Gotlib, 2015; Marchetti, Koster, Sonuga-Barke, & De Raedt, 2012; Marwood, Wise, Perkins, & Cleare, 2018; Wang, Ongur, Auerbach, & Yao, 2016). Both networks are considered to be neural hubs of high importance because of their proposed role in enabling interactions between control and processing systems, allowing integration and flexible regulation of attention, cognition, emotion, sensory experience and behaviour (Gordon et al., 2018; Downar et al., 2018, Power et al, 2013). In particular, the salience network plays a central role in attention and emotion

regulation and in integrating and filtering interoceptive, autonomic and emotional information (Downar, Blumberger, & Daskalakis, 2016), whereas the default mode network is associated with a broad range of states, including social cognition, self-referential processes and during depression the inability to disengage from ruminative and negatively biased thought patterns (Wang et al., 2016). Both networks have been implicated in depressive symptomology, prediction of treatment response (Lythe et al., 2015; Marwood et al., 2018; McGrath et al., 2013; Posner et al., 2013) and found to respond to mindfulness training in healthy participants (Doll, Holzel, Boucard, Wohlschlager, & Sorg, 2015; Farb et al., 2010; Tang, Holzel, & Posner, 2015; Vignaud, Donde, Sadki, Poulet, & Brunelin, 2018; Yang et al., 2019; Young et al., 2018). There is, however, a general lack of research on the neural mechanisms of mindfulness for depression, and specifically on how neural connectivity and concurrent psychological processes may change as a function of MBCT treatment amongst patients with recurrent major depressive disorder (Davidson, 2016; Van der Velden & Roepstorff, 2015).

Here we present the first fMRI study looking at the neurocognitive mechanisms behind effective MBCT treatment of recurrent depression, and concurrent psychological processes. The fMRI paradigm consisted of wakeful rest, and states where mindfulness and rumination were induced, followed by experiencing sampling and questionnaires examining cognitive and affective experiences and depressive symptomology. To constrain the number of neural networks examined in this study, we selected the default mode network and salience network as priori networks of interest. Employing a randomized controlled design, we first confirmed the clinical efficacy of the treatment and the effectiveness of the mindfulness and rumination paradigm in modulating negative thoughts and body awareness. We then examined changes in neural connectivity and concurrent psychological processes during the three states (rest, mindfulness, rumination) as a function of treatment.

RESULTS

Between February 2017 and February 2018, 107 participants were assessed for eligibility, of which we recruited 80 patients. Of these, 50 participants were randomly allocated to receive MBCT in addition to treatment as usual (TAU) and 30 participants to TAU. Primary outcome data were obtained for 48 (96%) participants in the MBCT +TAU group and 28 (93%) participants in the TAU group at baseline. Participant flow over the study period with attrition and reasons are shown in figure 1. Of particular interest here, we obtained pre and post treatment FMRI scans from 68 participants (41 MBCT, 27 TAU). The rumination condition of the fMRI paradigm was voluntary due to ethical reasons, and we therefore only obtained both FMRI scans from 48 participants (28 MBCT, 20 TAU).

Baseline characteristics were balanced between the two groups on all demographic and psychiatric variables (Table 1). Of the 8 sessions, the mean attendance was 6.75 sessions with 94% attending at least 4 sessions.

Figure 1: Participant flow

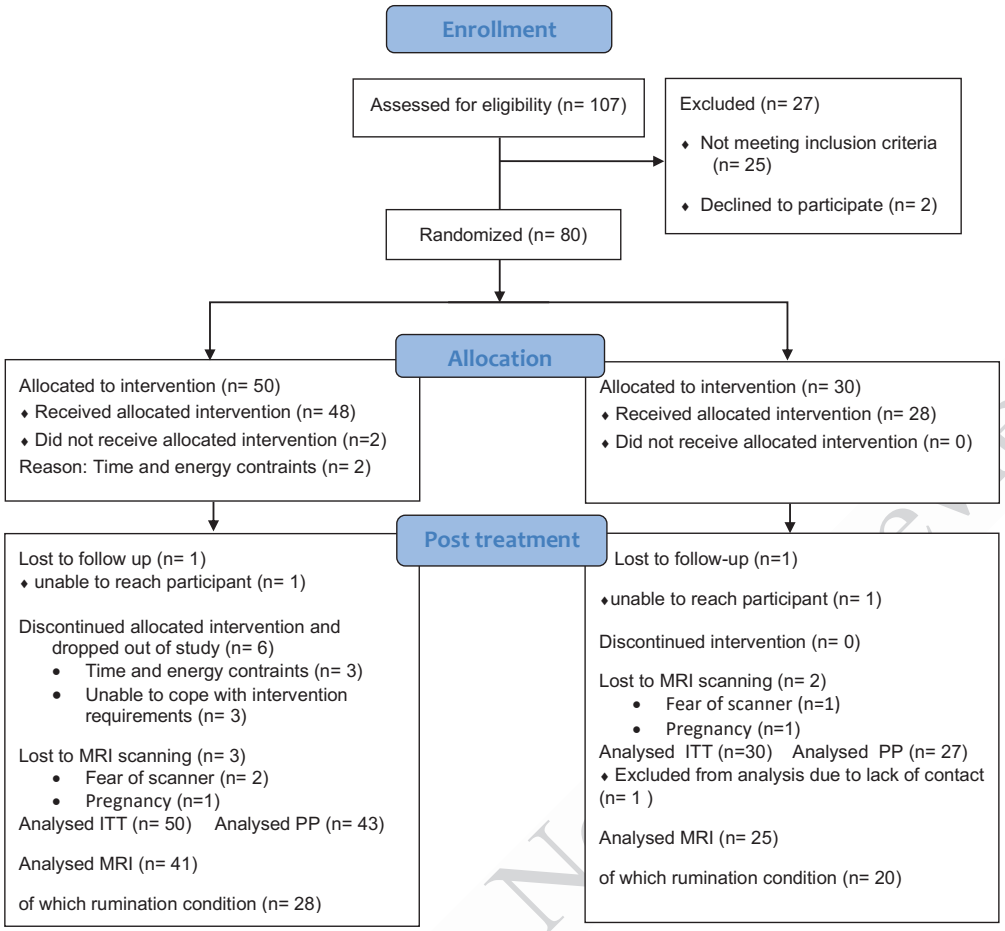

Table 1: Baseline Characteristics:

	MBCT+TAU	TAU
Age	43.17 (14.10)	45.25 (11.83)
Gender	70% female	82% female
On maintenance antidepressants	72%	89%
History of childhood trauma	59%	59%
Depressive symptoms (QIDS)	9.23 (4.58)	9.68 (5.10)
EQ	31.43 (7.12)	31.26 (7.06)
FFMQ	44.21 (8.88)	45.33 (8.02)
RRS	53.38 (9.80)	57.51 (8.24)
MAIA-Emotional awareness	15.32 (3.51)	16.57 (4.23)
MAIA-Body listening	6.25 (2.07)	7.40 (3.25)
MAIA-Attention regulation	17.22 (5.03)	17.78 (4.99)
MAIA-Noticing	12.79 (2.61)	13.96 (3.38)
MAIA-Trusting	8.89 (3.31)	8.40 (3.77)
MAIA-Not distracting	9.17 (2.64)	9.01 (2.45)

Table 1. Means with standard deviations in brackets or percentage of baseline characteristics and questionnaire scores for each group.

Clinical and behavioural assessments

Clinical efficacy

As manipulation checks we first set up to examined clinical efficacy. MBCT treatment significantly reduced depressive symptoms (SE= 1.18, CI -6.47-1.78, g= 0.82, p= 0.001) with a large effect size, whereas no change was found in the control group (Figure 2A). Attendance to the MBCT program (SE=14, CI: .20 - .76, g=.44, p=.001) and weekly practice (SE =0.06, CI: .02 - .26, g=.31, p=.022) moderated depression scores post treatment.

Figure 2: ***Change in depressive symptoms as a function of treatment***

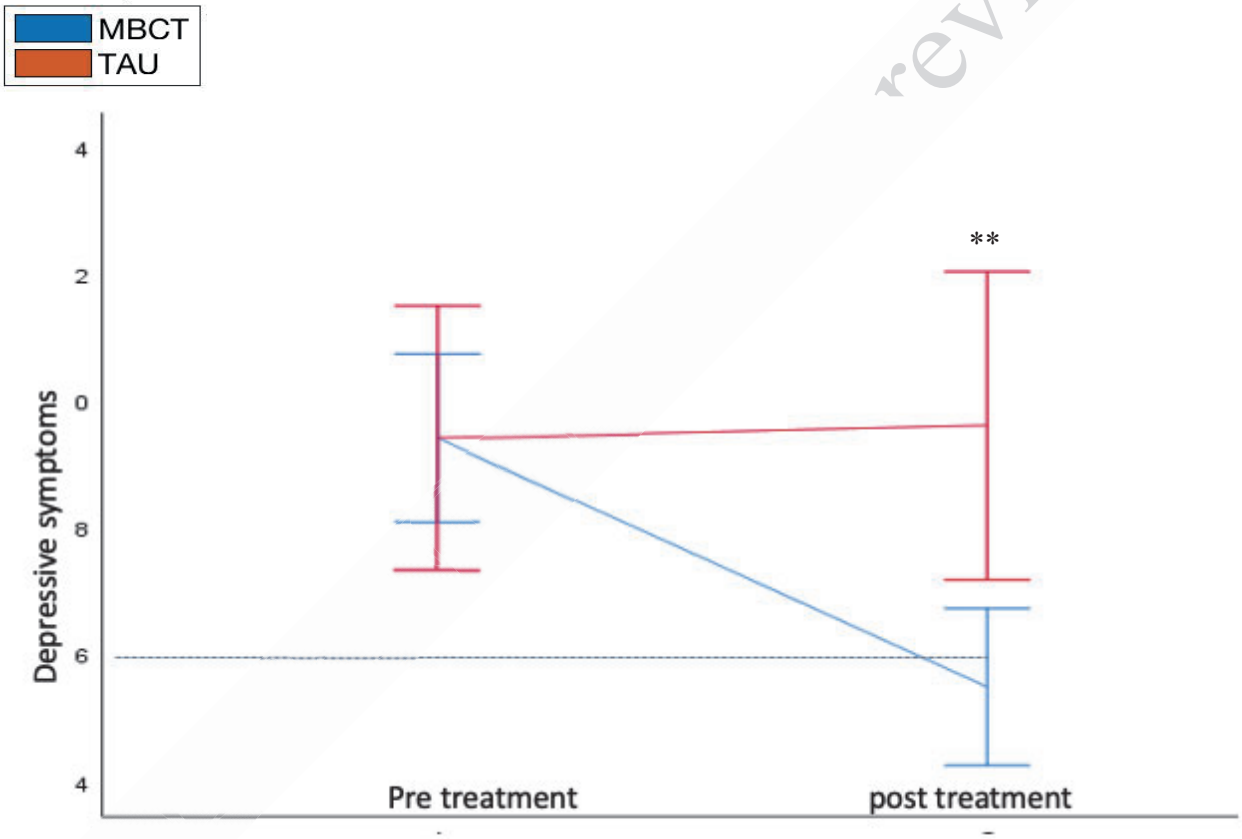

Figure 2. Depressive symptoms as a function of treatment. MBCT treatment (blue) caused a significant decrease in depressive symptoms QIDS-SR (Quick Inventory of Depressive Symptoms-Self Report (Rush et al., 2003) (p>0.001, g =0.82), whereas TAU control (red) did not change. Severity: 0-5=No depressive symptoms, 6-10=Mild depressive symptoms, 11-15=Moderate depressive symptoms, 16-20=Severe depressive symptoms, 21-27=Very Severe depressive symptoms. Error bars show 95% confidence intervals. *p<0.05, **p<0.01 comparing the groups.

Psychological change processes

To measure psychological processes hypothesized to be impacted by MBCT training we included questionnaires assessing multiple dimensions of interoceptive awareness, mindfulness skills and metacognitive awareness or decentering, and ruminative traits.

Interoceptive Awareness

We used a number of pre-selected subscales from the Multidimensional Assessment of Interoceptive Awareness (MAIA) (Mehling et al., 2012) to measure interoceptive awareness (figure 3). Compared with the TAU control group, individuals with recurrent depression receiving MBCT reported an increased ability to notice bodily sensations (MAIA -noticing subscale ($p<.001$, $g= 0.95$, CI [1.60-4.76]), awareness of the manifestation of emotions in the body (MAIA -emotional awareness subscale ($p<.001$, $g= 1.10$, CI [2.82, 7.12]); active listening to the body for insight (MAIA -body listening subscale ($p<.001$, $g= 1.19$, CI [1.63-3.85]) and the ability to sustain and control attention to body sensations (MAIA: attention regulation ($p<.001$, $g= 1.00$, CI [2.56-7.44]).

We found no significant interaction effects on the subscales of the experience of one's body as safe and trustworthy (MAIA – trusting subscale) and the tendency not to ignore or distract oneself from sensations of pain or discomfort (MAIA - not distracting subscale).

Figure 3: Change in Multiple Dimensions of Interoceptive Awareness (MAIA) as a function of treatment

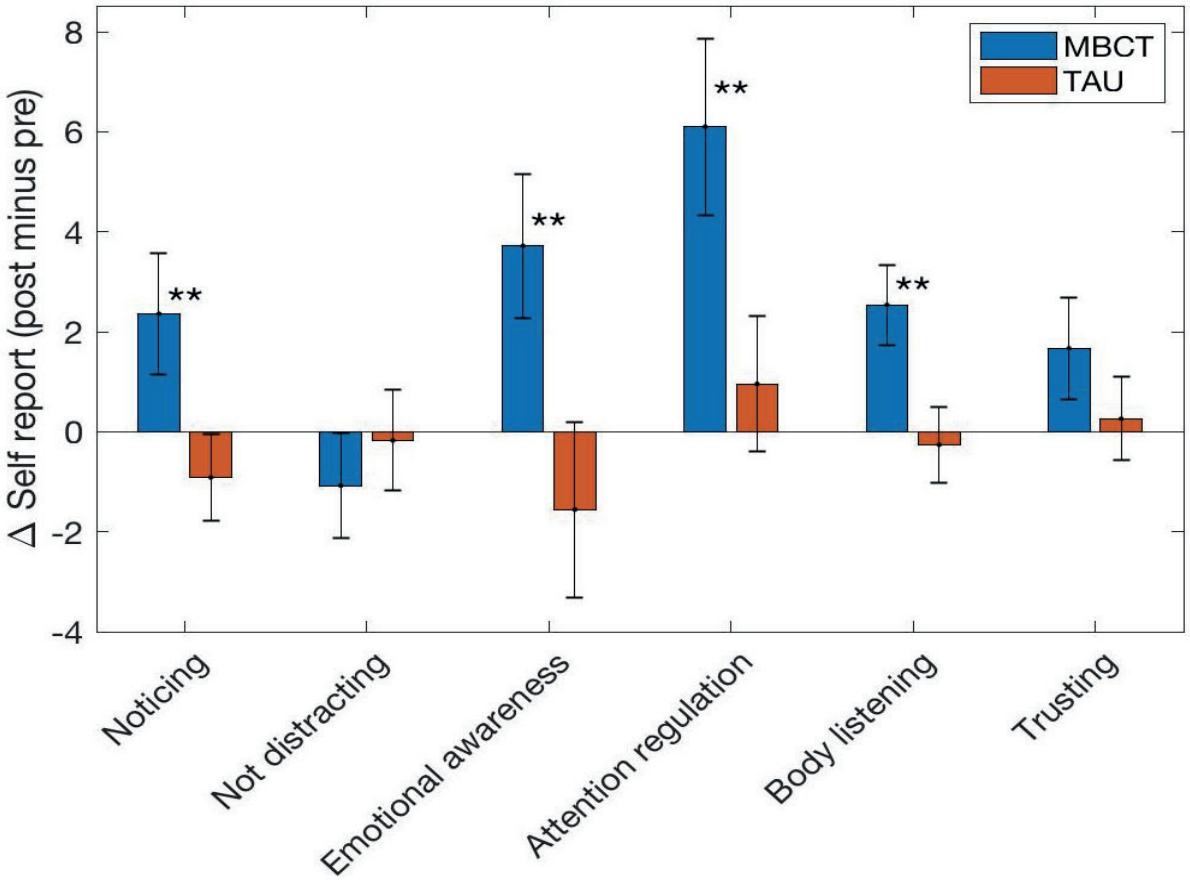

Figure 3: Subscales of the Multidimensional Interoceptive Awareness Questionnaires (MAIA (Mehling et al., 2012) differences between post and pre-treatment on preselected subscales of a) Noticing: Awareness of uncomfortable, comfortable, and neutral body sensations; Not-Distracting: Tendency not to ignore or distract oneself from sensations of pain or discomfort; Attention Regulation: Ability to sustain and control attention to body sensations; Emotional Awareness: Awareness of the connection between body sensations and emotional states; Body Listening: Active listening to the body for insight; Trusting: Experience of one's body as safe and trustworthy. MBCT caused increases on all subscales, apart from the 'not distracting' subscale. Error bars show 95% confidence intervals. *p<0.05, **p<0.01 for t-tests comparing the groups.

Decentering
We used the Experience Questionnaire (Fresco et al., 2007)) to measure decentering i.e. the ability to observe thoughts and feelings as temporary and automatic events in the mind, rather than facts or true descriptions of reality. Compared with the TAU control group, individuals with recurrent depression receiving MBCT reported increased decentering (EQ) (p<.001, g=0.98, 95% CI [3.76d, 11.01]).

Mindfulness
Five Factor Mindfulness Questionnaire (Baer et al., 2008) measured sensory awareness, awareness of actions and thoughts, as well attitudes of acceptance and non-reactivity. Compared with the TAU control group, individuals with recurrent depression receiving MBCT reported increased mindfulness (FFMQ) (p<.001, g= 0.68, CI [1.49, 9.57]).

Rumination
Rumination Response Scale (Treynor et al., 2003) measured trait rumination. We found no significant interaction effects on the ruminative response scale measuring trait rumination neither as full scale nor as subscales, i.e. brooding, reflection and depression.

Neural results

Manipulation check of fMRI paradigm

The study design was tailored to address how MBCT can affect general vulnerability (resting state), a mindfulness meditation state (proposed mechanism), and a state in which cognitive vulnerability to relapse was induced (rumination). The rumination state was designed to trigger a situation of vulnerability (i.e. inducing ruminative thought patterns by asking participants to recall a negative autobiographical event and reflect on how it related to themselves and their role in it) that were likely to induce ruminative negative thought patterns. The mindfulness state on the other hand was designed in induce awareness of present-moment embodied experiences (see method section for full description of the manipulations). To check that the manipulated states were effective in modulating negative self-related thoughts and body awareness, we asked participants about their cognitive and affective experiences after each scan (See details in supplements) As expected, rumination strongly increased negative self-related thoughts and decreased body awareness compared to all other conditions (figure 4A, all p<0.01). In contrast, mindfulness induction led to

fewer negative self-related thoughts and increased body awareness compared to all other conditions.

Focusing on the rumination condition (figure 4B, other conditions in figure S1), we found that MBCT compared to TAU did not significantly change experiencing sampling reports of body awareness (t(47)=-0.18, p=0.86, Hedge's g=-0.05 [CI: -0.62 – 0.52]) or negative self-related thoughts (t(47)=0.39, p=0.39, Hedge's g=-0.25 [CI: -0.82 – 0.33]) reported after rumination.

Figure 4: Change in experience sampling after each state

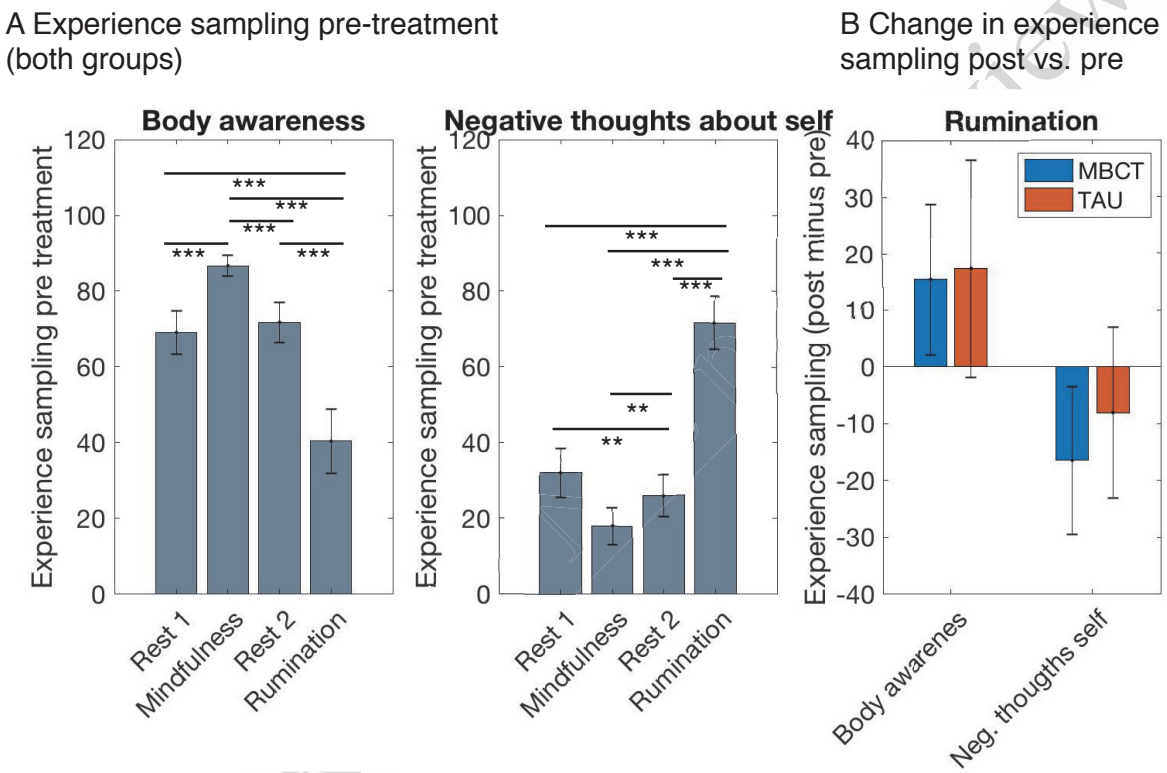

Figure 4. Experience sampling after each scan. A) Experience sampling pretreatment (both groups combined). The different scan conditions affected the responses to the experience sampling. After the rumination scan, participants reported less body awareness and more negative thoughts about themselves than after either rest or mindfulness. B) Experience sampling changes as a function for treatment (post minus pre) for the rumination conditions. There was no significant effect of treatment for responses after the rumination scan. Changes for other conditions are shown in figure S2. Error bars show 95% confidence intervals. *p<0.05, **p<0.01, ***p<0.0001, significance stars show in (A): within subject t-tests comparing the different scan conditions; in (B) no t-tests comparing the groups reached significance.

Change in neural connectivity as function of treatment

To examine whether treatment changed neural connectivity between the default mode network and the salience network (figure 5A) and the rest of the brain, we examined group x time interactions across the four scan conditions (i.e. resting state 1, mindfulness induction, resting

state 2, and rumination induction)). For the default mode network, we found no significant group x time differences. For the salience network, we found that connectivity was changed during the rumination condition (n=48) as a function of treatment. In particular, we found changes in salience network connectivity with both the right lingual gyrus and the left lateral occipital cortex (lingual gyrus: x=14, y=-64, z=0, extend: 85 voxels, max. t-value: 6.25; lateral occipital cortex: x=-52, y=-82, z=16, extend: 16 voxels, max. t-value: 5.93; $p<0.05$ with FWE Bonferroni correction for two-sided test and testing across two a priori networks $p< 0.0125$) (Figure 5B).

Subsequently, we tested whether the group differences (MBCT vs. TAU) were present pre intervention or post intervention (figure 5C). We found that the groups did not differ pre treatment (occipital: Mann-Whitney U=396, p=0.19, rank biserial correlation=0.2, nMBCT=31, nTAU=21; lingual gyrus: Mann-Whitney U=374, p=0.374, rank biserial correlation=0.149). Instead, the MBCT group showing reduced connectivity post treatment between salience network and both regions of occipital cortex (Mann-Whitney U = 134, p=0.001, rank biserial correlation= 0.538) and lingual gyrus (Mann-Whitney U = 152, p=0.004, rank biserial correlation=0.476); for completeness see supplements (S2) for other scan conditions.

Figure 5: ***Change in neural connectivity as a function of treatment***

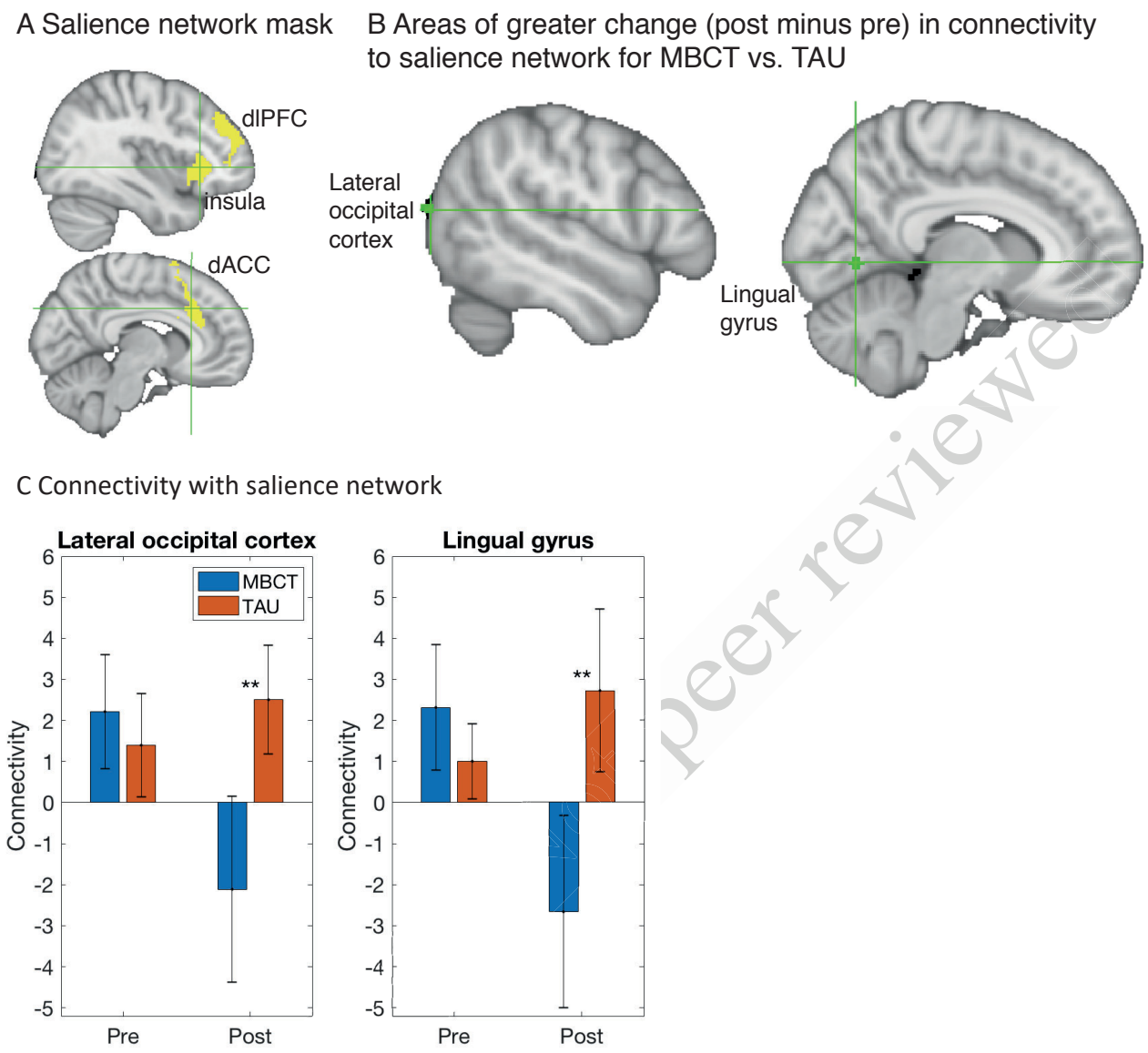

Figure 5. Change in neural connectivity as a function of treatment. A) The mask for the salience network (SN) included the dorsal anterior cingulate cortex, the dorsolateral prefrontal cortex and the anterior insula. B) Comparing the effect of MBCT vs. TAU on change in connectivity (post minus pre MBCT/TAU) with SN. Connectivity is changed to the lateral occipital cortex and the lingual. C) Connectivity between SN and lateral occipital cortex (left) and lingual gyrus (right) separately for pre and post treatment and for the MBCT (blue) and the control group (red). In both areas, MBCT decreased the connectivity to SN compared to TAU post treatment while there was no difference between the groups pre-treatment. Error bars show 95% confidence intervals. *p<0.05, **p<0.01 for two-tailed t-tests comparing the two groups.

Relating neural connectivity during rumination to self-reported psychological processes

To understand how changes in neural connectivity and psychological processes were related, we correlated changes in connectivity between salience network and the lingual gyrus and occipital cortex to changes in questionnaire and experience sampling scores. We analyzed the whole

sample correcting for multiple comparisons and for group using partial correlations to access robust relationships that would not just be a marker of treatment effect. We found that connectivity change between salience network and lingual gyrus was associated with self-reported interoceptive awareness - attention regulation subscale (MAIA), in which higher ratings on attention regulation abilities related to more decoupling of the salience network to the lingual gyrus (figure 6A, partial correlation [controlling for group]: n=44, r=-0.55 [CI; -0.73 - -0.31], p=0.0001, [with family-wise error correction for total of 40 tests, p-threshold for Bonferroni correction is p<0.0013]). This correlation was also found separately in the MBCT (n=26, r=-0.54 [CI:-0.77 - -0.19], p=0.004) and the TAU (n=18, r=-0.63 [CI: -0.84 - -0.22], p=0.006) groups. No other partial correlations reached significance when correcting for multiple comparisons.

Examining the relationship between treatment, neural change and psychological processes further revealed that the increased ability to sustain and control attention to body sensations mediated the relationship between treatment and neural change (figure 6B, mediation coefficient [a*b]: 3.51 [CI: 1.43-6.95], p=0.0001).

Figure 6: ***Associations between change in neural connectivity and change in concurrent psychological processes***

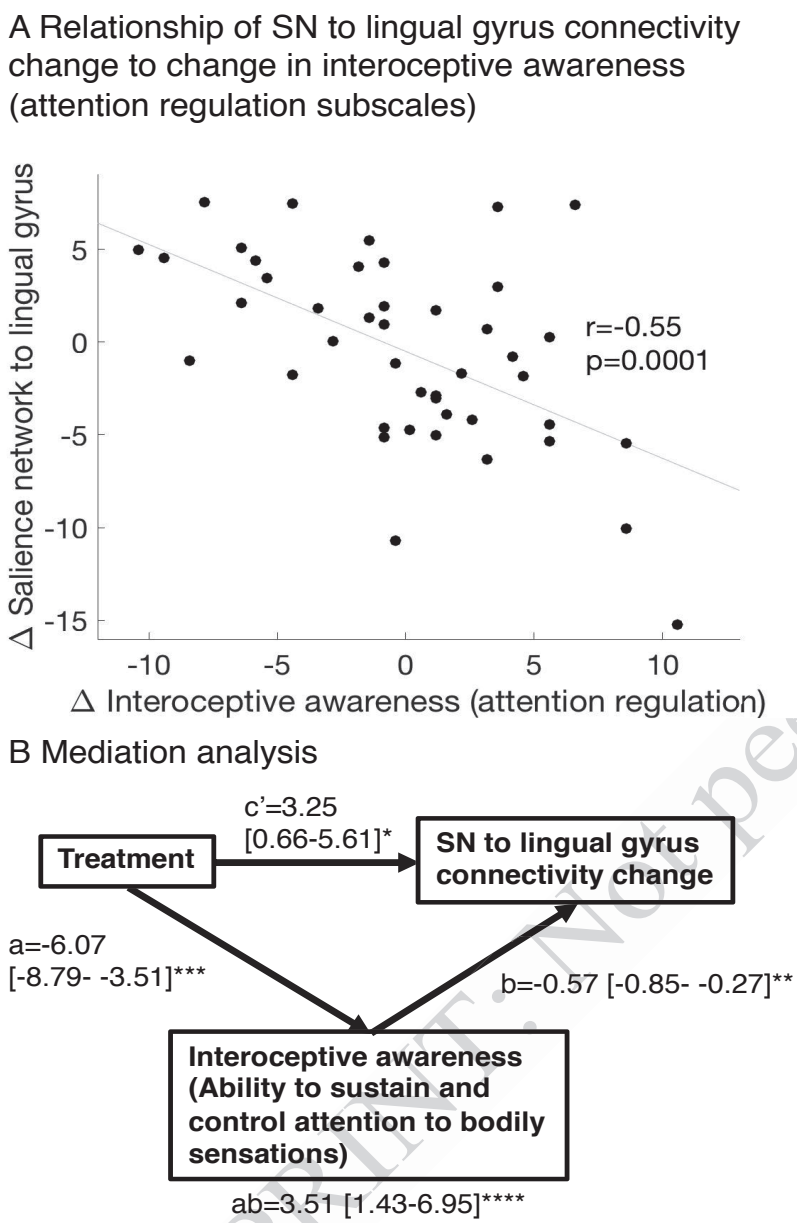

Figure 6. **Associations between change in neural connectivity and change in concurrent psychological processes** A) Partial correlation between the connectivity change (post minus pre) for the SN to lingual gyrus and change in self-reported interoceptive awareness on the Multi-Dimensional Assessment of Interoceptive Awareness (MAIA) (attention regulation subscale), controlling for treatment group. B) Mediation analysis. The effect of treatment on the decrease in connectivity between SN and lingual gyrus is mediated by increases in self-reported ability to sustain and control attention to body sensations. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 for significance of the paths in the mediation model.

DISCUSSION

Mindfulness-Based Cognitive Therapy (MBCT) is an effective treatment for recurrent depression, but little is known about its neurocognitive mechanisms of action. Here we present the first fMRI study looking at the neurocognitive mechanisms of effective Mindfulness-based Cognitive Therapy

(MBCT) treatment of recurrent depression and concurrent psychological processes, employing a randomized controlled design. We first confirmed the clinical efficacy of the treatment and the effectiveness of the rumination paradigm in modulating negative thoughts and body awareness. We then investigated the underlying neurocognitive mechanisms across the three states (rest, mindfulness, rumination). MBCT compared with treatment-as-usual led to decreased functional connectivity between salience network connectivity and both lingual gyrus and occipital cortex during the ruminative state. No change was found in the mindfulness and resting states, nor in the default mode network seed, as a function of treatment. Change in salience network connectivity was mediated by the ability to sustain and control attention to body sensations. These concurrent neural and psychological changes may be a mechanism by which MBCT works at times of high vulnerability to relapse, but may also point to universal pathways by which mindfulness meditation foster mental health benefits.

Our findings are consistent with a growing body of literature indicating a central role for the salience network in depression symptomology and treatment response (Downar et al., 2016; Fox et al., 2014; Godlewska et al., 2018; Lythe et al., 2015; Marwood et al., 2018; McGrath et al., 2013) Activation in areas of the salience network, such the anterior circulate cortex (ACC) and the insular cortex, have been found to predict treatment response across various form of psychotherapy for depression (Marwood et al., 2018), change in response to mindfulness-based interventions across a wide group of populations (Tang et al., 2015; Young et al., 2018), and modulate depressive symptoms after mindfulness training amongst healthy participants (Farb et al., 2010). During depression, the lingual gyrus has amongst others been associated with episodic memory (Kukolja, 2016) and emotional processing (Cornelly et al., 2017), whereas the occipital cortex has been associated with visualization of painful experiences, memory retrieval and emotional processing (e.g.Teng et al., 2018). The change in salience network connectivity and in the ability to regulate ability to sustain and control attention to body sensations might relate to the core skills of MBCT of recognizing and decoupling from conditioned patterns of ruminative negative thought by shifting the attentional focus to the body.

Our experiencing sampling data showed that the rumination state led to a large increase in negative self-related thoughts, and a simultaneous decrease in body awareness compared to the resting state or the mindfulness state. However, we did not find evidence of a reduction in negative self-related thoughts as a function of treatment. Perhaps this is not surprising given that the mindfulness techniques taught in the MBCT program do not focus on changing thought content, but rather on changing the extent to which individuals with recurrent depression become aware of and identify with negative thought patterns, once activated, and consequently how likely they are to become stuck in a ruminative mind state that may lead to a downwards spiral of depressive mood and potential onset of relapse (Segal, Williams, & Teasdale, 2013) The lack of change found in ruminative trait scores and DMN connectivity may support this premise, given that several studies have linked abnormal default mode network connectivity to ruminative and self-referential thought patterns during depression (e.g. Hamilton et al., 2015; Wang et al., 2016).

The study has a number of methodological strengths. First, the study design was tailored to address how MBCT can affect general vulnerability (resting state), a mindfulness meditation state

(proposed mechanism), and a state in which cognitive vulnerability to relapse was induced (rumination), and the RCT design allowed us to evaluate neural changes caused by MBCT treatment. The study complied with recommendations posed by recent reviews of the neuroscience of mindfulness and mechanisms of MBCT, included assessing theoretically relevant and clinically informed mechanisms, triangulating across self-report, clinical and neural measures and including both resting states and experimental manipulation of neurocognitive states to access the effects of both mindfulness practice and emotion regulation (Davidson, 2016; Tang et al., 2015; van der Velden et al., 2015; Vignaud et al., 2018; Young et al., 2018). Furthermore, the study limited accessor bias through masked outcome assessment, and we ensured that the intervention had high fidelity, by delivering the intervention according to the treatment protocol from highly experienced teachers and ensuring high treatment adherence, engagement and retention from participants.

The study also had a number of limitations. We chose treatment as usual as control group, as we wanted to know how the intervention of MBCT as a whole effect neural change, and whether such neural change predict relapse risk. This characteristic of the study is both a strength (generalizability, external validity) and a limitation (lack of specificity). In the absence of an active control group we cannot infer whether the treatment effects are specific to MBCT treatment or whether other effective depression treatments may yield similar effects. Future research could investigate treatment specificity by comparing MBCT to equally effective treatments, and the extent to which the mindfulness meditation practices of MBCT drives the neural change by employing a dismantling design or an active attention control. Out of ethical reasons, participants could opt of the rumination condition, meaning that the neural findings can only be generalizable to participants willing to participate in the rumination induction. However, in terms of clinical outcomes we found no difference (i.e. both improved) in efficacy for the people participating in the rumination induction and the ones who did not.

Our findings suggest that MBCT changed neural connectivity during a rumination state rather than during general resting state or a mindfulness state, even though we had a smaller sample (N=48) completing the rumination condition. Shifting the focus of future research to mind states characterized by of high vulnerability to relapse rather than during resting states, may have potential to increase our understanding of how to optimize preventative treatments to depressive relapse.

CONCLUSION

Mindfulness-based Cognitive Therapy compared with treatment as usual led to reduced depressive symptoms and decreased functional connectivity between salience network connectivity and lingual gyrus and occipital cortex during a ruminative state. Change in salience network connectivity was mediated by the ability to sustain and control attention to body sensations, suggesting that salience network plasticity during depressive rumination is related to embodied attention regulation capacity. These changes may be a mechanism by which Mindfulness-based Cognitive Therapy works to increase resilience and reduce vulnerability to relapse.

METHODS

Study design and participants

We set up a single-blind, parallel randomized controlled trial examining neural mechanisms of change and concurrent psychological processes in MBCT+ TAU and TAU. The study design including primary, secondary outcomes and study procedures were preregistered in November 2017 with a revised specification of the a priori networks in December 2018 before running analyses based on new literature reviews in the field (ClinicalTrials.gov Identifier: NCT03353493). The original and updated study protocol was approved by the Regional Ethics Council and is available at the study website. This study reports the primary i.e. neural outcomes, proximal clinical outcomes and psychological process outcomes that was part of the randomized controlled design in the trial registration. Embedded in the trial registration was studies of molecular biomarker outcomes, stress and an emotional bias task, and distal clinical outcomes with a different author group, to be reported in future papers.

Participants were recruited from general practices at local psychiatric units in the region of Midtjylland in Denmark. Inclusion criteria were a diagnosis of recurrent major depressive disorder with or without a current episode; three or more previous major depressive episodes; age 18 years or older and, if on antidepressants, a stable dose of SSRI or SNRI medication for a minimum of 8 weeks. Exclusion criteria were a current severe major depressive episode, a history of schizophrenia, schizoaffective disorder, bipolar disorder, current severe substance abuse, organic mental disorder, current/past psychosis, pervasive developmental delay, persistent antisocial behaviour, persistent self-injury requiring clinical management/therapy; formal concurrent psychotherapy; having previously completed MBCT/MBSR training and/or extensive meditation experience (i.e. retreats or regular meditation practice); anti-psychotic medication and benzodiazepines. All participants gave written informed consent.

Most participants self-referred as per recommendation from their general practitioner or psychiatrist. The study was also advertised in the local community and at Aarhus University, and interested patients could therefore self-refer.

The study protocol was approved by the the regional ethics committee in Region (ID: 1-10-72-259-16: 66534) and registered at the Danish Data Protection Agency (2016-051-000001). The trial was conducted and reported in accordance with CONSORT guidelines for reporting of Randomized Controlled Trails (Schulz, Altman, & Moher, 2010)and COBIDAS guidelines from the Organization for Human Brain Mapping's 'Statement on Neuroimaging Research and Data Integrity' (Nichols, 2016)

Randomisation and masking

Participants (N =80) were randomly allocated (in a 5:3 ratio) to receive either an 8-week MBCT class +TAU treatment or adhere to TAU treatment. Patients were randomly assigned by an independent researcher to the two groups with a computer-generated random number sequence stratified according to antidepressant use and participants' symptomatic status at randomization

using the BDI-II Beck Depression Inventory -II (Beck, Steer & Brown, 1996) of less than 13 being asymptomatic, and greater than or equal to 14 being symptomatic. Research assessors conducting clinical interviews and MRI scans were masked to treatment allocation for the duration of the follow-up period, and questionnaires were administered online. Patients were masked to treatment allocation at baseline assessment, but given the nature of psychological treatment, patients and clinicians were made aware of treatment allocation after baseline assessment.

Intervention and procedures

MBCT

MBCT is a manualized group-based program aiming to teach participants skills to prevent relapse or recurrence of depression(Segal et al., 2013). MBCT integrates psychoeducation elements from cognitive behavioral therapy for depression with a systematic training in mindfulness meditation techniques from mindfulness-based stress reduction (MBSR) program. MBCT was taught in accordance with the manual and consisted of a pre-class interview, weekly classes of 2.25 h during an 8 weeks period with homework and 4 booster sessions offered every 3 months after the program. Two highly experienced therapists delivered 4 MBCT groups in university settings. The therapists were instructors in MBCT with at least 7 years' experience.

TAU

TAU can consist of antidepressant medication and psychological therapy. We restricted TAU to no psychotherapeutic intervention and either a stable dose antidepressant medication or no medication at the time of treatment to enable to us draw conclusions of the effect on MBCT. Participants were asked every 3 months to report potential changes in TAU treatment. We encouraged all participants to adhere to TAU medication for the full length of the trial. However, patients remained in the trial whatever treatment choices they made. Originally, TAU participants were offered MBCT once data collection was over, however this was modified to 6 months post randomisation out of ethical considerations and to avoid a large drop-out in the control group, as MBCT is not readily available as treatment in Denmark, and as many participants were not responding sufficiently to their current treatment and suffered residual symptoms. However, the TAU group still completed all follow up measurements.

PROCEDURE

All participants were assessed at baseline (before randomization) and within 1 month after the end of the 8-week MBCT program.

MEASURES AND PROCEDURES

CLINICAL OUTCOMES

Depressive symptoms. We measured depressive symptoms using the Quick Inventory of Depressive Symptomology (QIDS_SR (Rush et al., 2003)). Participants were assessed at baseline (before randomization) and within 1 month after the end of the 8-week MBCT program

Questionnaires

Interoceptive Awareness: We measured Interoceptive Awareness at baseline and within a month after treatment using the Multidimensional Assessment of Interoceptive Awareness (MAIA) (Mehling et al., 2012). We did not include the full questionnaire, but preselected the subscales of noticing, emotional awareness, body listening, attention regulation, trusting and not-distracting.

Decentering: We measured decentering at baseline and within a month after treatment using the Experiences Questionnaire – decentering subscale (Fresco et al., 2007).

Mindfulness skills: We measured mindfulness skills at baseline and within a month after treatment using the Five Factor Mindfulness Questionnaire, FFMQ (Baer et al., 2008).

Rumination: We measured trait rumination at baseline and within a month after treatment using the Rumination Response Scale (Treynor et al., 2003).

Neural connectivity

The primary mechanisms outcome measure was change in neural connectivity measured by fMRI. As a priory networks of interest, we selected the Default Mode Network (DMN) and the Salience Network (SN).

Power analyses of fMRI studies are not used routinely, and, in the current case, there were insufficient information to perform a specific calculation. However, there is widespread consensus that to detect a small to moderate effect size, 20 to 30 participants per group is an optimal number (Desmond & Glover, 2002; Mumford, 2012). We originally aimed for the conservative end of the spectrum with 30 in each group, allowing for up to 20 % attrition. During recruitment and before randomization, it was decided to increase the number of participants to 50 in the MBCT group to allow more statistical power for mediation and prospective analyses.

MRI paradigm

The MRI paradigm included a structural scan and four separate functional connectivity scans (5 minutes each) in the consecutive order of resting state I, an instructed mindfulness state, resting state II, and an instructed rumination state. The paradigm was pilot tested for understanding of the procedures and questions, and acceptability in terms of content and duration.

Each state was followed by experience sampling in the scanner, assessing affective,

cognitive and somatic experiences with the purpose of i) validating the mindfulness and rumination states and ii) assessing how cognitive and affective content correlate with brain dynamics, adapted from work by (Smallwood et al., 2016). The rating items were presented on a computer screen in the scanner using a Visual Analogue Scale (VAS) scale with statements shown in the middle of the screen and a scale were the degree of agreement from 0- 100% could be indicated by moving a cursor on the scale with a trackball. See Appendix 1 for full list of questions.

Resting state instructions
During resting states, participants were told to relax and close their eyes.

Rumination induction instructions

Participants were guided through a rumination induction adapted from a paradigm by (Karl, Williams, Cardy, Kuyken, & Crane, 2018) in which participants first rehearsed a sad autobiographical memory and subsequently were instructed to stay with their sad mood and reflect on self-related causes and consequences of their low mood (See (Karl et al., 2018) for detailed description). Using a negative autobiographical memory to induce sad mood and ruminative thought patterns is well-established method in the field (Karl et al., 2018; R.E., R.A., & Segal, 2011; Segal et al., 2013). It was possible for participants to opt out of the rumination condition, if they felt it would be too stressful for them.

Mindfulness meditation instructions

During the mindfulness meditation state, participants were guided through a well-established mindfulness exercise, the 'breathing space', which is used in the MBCT program. First participants were instructed to become aware of the present moment's thoughts, feelings and bodily sensations. Then they were guided to direct the attention to the sensation of the breath and, finally, to expand the awareness to the body as a whole including the embodied manifestations of emotions, thoughts and bodily sensations. Throughout the mindfulness exercise, embodying an attitude of curiosity and acceptance was encouraged.

Participants were scanned at baseline and within a month after treatment.

PREPROCESSING AND ANALYSES

MRI scan protocol

All participants were scanned at 3 Tesla Siemens Magneton Skyra 3T scanner (Siemens, Erlangen, Germany). BOLD-fMRI: Gradient-echo (*TE*=40/*TR*=3,000 ms) with single-shot 2D echo planar imaging readout; spatial resolution=3.8 × 3.8 × 3.8 mm^3, 52 slices, repetition time: 1.48 s, slice thickness, in-plane resolution, field of view: 64 x 64 matrix, echo time: 30 ms.

FMRI preprocessing

We used FSL tools (Smith et al., 2004) for preprocessing. Preprocessing steps followed

standard procedures and included: skull-stripping (BET tool (Smith, 2002) registering the functional to the structural image (FLIRT tool (Jenkinson, Bannister, Brady, & Smith, 2002) with default settings for Boundary-Based registration), registering the structural image to standard space (FNIRT tool (Andersson, 2007) with default settings for 12 degrees of freedom and warp-resolution of 10mm), motion correction (MCFLIRT tool (Jenkinson et al., 2002) and spatial smoothing of the data with 5mm kernel. We used Independent component analysis-based strategy for Automatic Removal of Motion Artifacts (ICA-AROMA (Pruim, Mennes, Buitelaar, & Beckmann, 2015). For further denoising, first five eigenvariates of time courses extracted from white matter and cerebrospinal fluid masks (segmentation was done using FAST tool (Zhang, Brady, & Smith, 2001) were removed (using fsl_glm). Finally, data was high-pass filtered (100 seconds cut-off).

Analytical methods

We applied the following analytical procedure: We first confirmed the clinical efficacy of the treatment and the effectiveness of the rumination paradigm in modulating negative thoughts and body awareness. We then examined changes in neural connectivity and concurrent psychological processes during the three states (rest, mindfulness, rumination) as a function of treatment, and finally whether change in psychological processes correlated or mediated neural change.

Clinical efficacy analyses

Effects on self-report clinical measures and questionnaires were analyzed with multilevel models (MLMs). In these models, time (level 1) was nested within individuals (level 2). *P*-values were two-sided, and MLMs were based on the intent-to-treat sample, thereby including all individuals with their completed observations. Intercepts were specified as random in all models, allowing for the estimation of a separate intercept for each individual. The slope was also specified as random if it significantly improved the model fit. Missing data at the item level were handled by mean substitution, which was only considered for participants with less than 50 % missing data on a particular scale. Cohen's *d* was derived from the F-parameter, calculated as $d=2\times\sqrt{(F/df)}$ and then transformed into Hedges' *g*. An effect size of 0.2, 0.5 and 0.8 was considered small, medium and large, respectively. All MLMs were performed in SPSS-25. We used Cox regression to access relapse risk.

Mechanisms analyses

To look at mechanisms and compare neural findings with psychological process findings, we also needed analyses using only complete cases. Using sensitivity analyses, we checked that MLM ITT and t-tests based on complete results lead to similar effect sizes and significance levels.

FMRI analyses

FMRI seed region extraction

To derive seed regions for the salience and default mode networks we used a previously published and widely used set of brain network maps (Yeo et al., 2011). For each participant, time courses were extracted for each network mask as first eigenvariate using fslmeants.

Group comparisons

We compared salience and default mode network connectivity with the rest of the brain as a result of treatment, i.e., group x time interactions, using complete cases. First, we obtained connectivity maps between the a priori networks and the rest of the brain using regression analysis with fsl_glm. Having obtained maps of regression weights, i.e. Contrast of Parameter Estimates (COPEs) per participant, condition, a priori network and timepoint, we looked at changes between post and pre-treatment, by subtracting pretreatment COPEs from post treatment COPEs.

We compared the randomized groups statistically per condition and a priori network using nonparametric permutation testing with threshold-free cluster enhancement (TFCE) from FSL's randomise (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). Results were thresholded at $p<0.05$ with Bonferroni family-wise error correction for two-tailed tests across the two a priori networks.

Relating neural connectivity to psychological processes via questionnaires and experience sampling measures

We related change in neural connectivity to changes in self-report measures using partial correlation analyses, controlling for group assignment using partial correlations to access robust relationships that would not just be a marker of treatment effect. We corrected for multiple comparisons across the number of significant neural findings (i.e. two ROIs) and the number of questionnaire measures tested (i.e. 20: 3 experience sampling questions [body awareness, thought awareness and negative thoughts about the self] and 17 questionnaires [QIDS, EQ, five subscales of the FFMQ, three subscales of the RRS questionnaire, six subscales of the MAIA questionnaire]). This meant $p<0.0013$ with Bonferroni correction. We also report full correlations separately for each group.

We used a meditation analysis to test whether the effect of treatment on change in connectivity from SN to lingual gyrus was mediated by increased ability to sustain and control attention to body sensations (Multiple Dimensions of Interoceptive Awareness Questionnaire - Attention Subscale, Mehling et al., 2012) using the Matlab 'M3 Mediation toolbox' (Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008).

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Supplements

S1: Experience sampling questions

Question/component	Resting state I+II	Mindfulness state	Rumination state
1.Manipulation check	**X**		
1.1 I felt asleep	**X**		
1.2 I kept my eyes closed	**X**		
1.3.I could follow the instructions	**X**	**X**	**x**
2. Awareness	**X**		
2.1.I was aware of my body	**X**	**X**	**x**
2.2.I was aware of my emotions	**X**		
2.3 I was aware of my thoughts	**X**	**X**	**x**
3. Affective and cognitive content	**X**		
3.1 I felt sad	**X**		
3.2 I felt happy	**X**		
3.3 I had thoughts about the past	**X**		
3.4 I had thoughts about the future	**X**		
3.5 I had negative thoughts about myself	**X**	**X**	**x**
3.6 I had positive thoughts about myself	**X**		

S2: Experience sampling body awareness and negative self-related thoughts all states

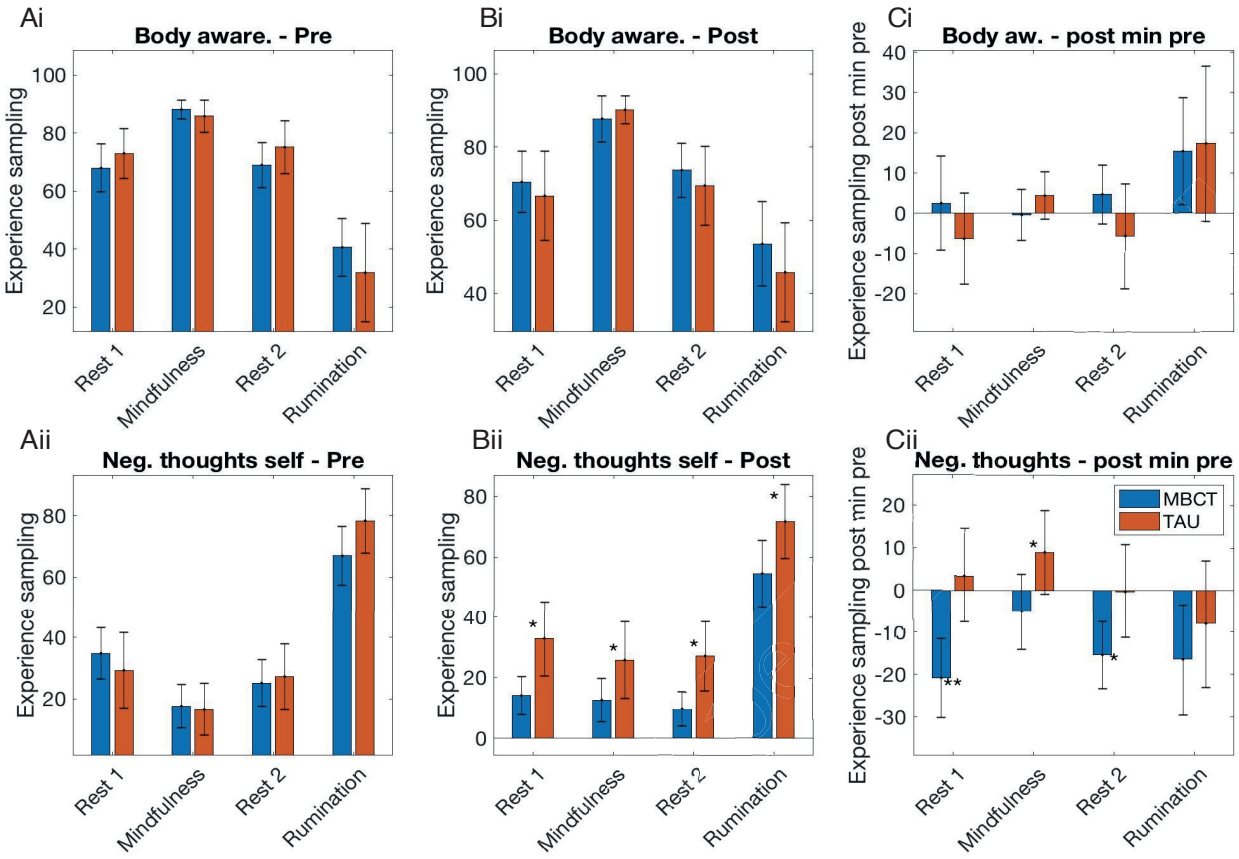
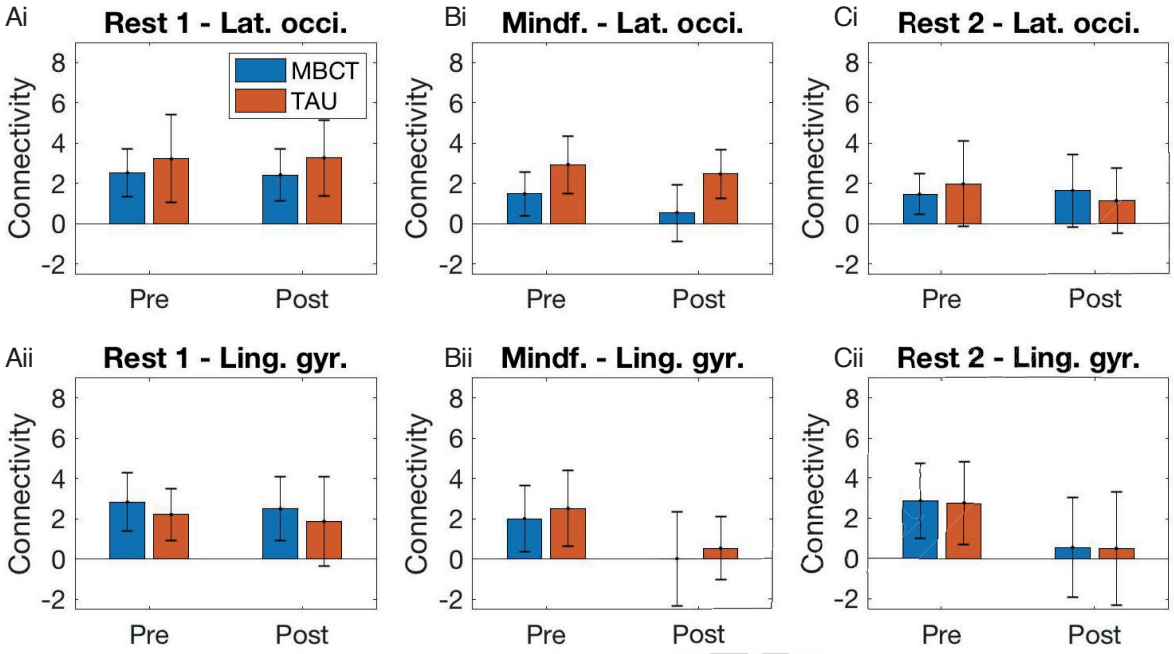


Figure S2. Pre-post experience sampling reports after each state. A: Pre-treatment, MBCT (blue) and TAU (red) groups do not differ in any post-scan self reports. B: Post-treatment, MBCT groups shows reduced negative thoughts about self in each scan, but not changes to body awareness. C: Comparison of treatment changes (post minus pre) in the two conditions. Indeed, self-reports differed after the intervention between the MBCT and the TAU group (2 (time) * 2 (question) * 2 (group) : interaction effect of pre/post*question*group: $F(1,47)=6.68$, $p=0.013$, $\eta^2=0.004$). Specifically, negative thoughts about self were reduced by MBCT across the four scan conditions (2 (time) * 2 (group) ANOVA for the negative thoughts about self question: interaction between pre/post*group: $F(1,47)=15.78$, $p<0.001$, $\eta^2=0.015$). Follow-up t-tests revealed that this was driven by reduced negative thoughts about the self during rest 1, mindfulness and rest 2, but not rumination. Self reports about body awareness were not changed by treatment after any of the scans. Results of uncorrected t-tests comparing the two groups shown, *p<0.05, **p<0.01.

S3: Salience network connectivity to lingual gyrus and occipital cortex during rest and mindfulness



Figures S3. Salience network connectivity. Salience network (SN) connectivity during rest 1 (A), mindfulness (B) and rest 2 (C), separately for each group, pre- and post-treatment and from SN to lateral occipital (i) and lingual gyrus (ii). No connectivity differed between the groups (t-tests at $p<0.05$, not correcting for multiple comparisons).