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

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ABSTRACT

Depression is a leading cause of disability worldwide and prevalence is on the rise. One of the most debilitating aspects of depression is the dominance and persistence of depressive rumination,- a state of mind that is linked to onset, and recurrence of depression. 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. In a randomized controlled fMRI study, we looked at the neurocognitive mechanisms behind Mindfulness-Based Cognitive Therapy (MBCT) treatment of recurrent depression. MBCT compared with treatment as usual (TAU) decreased functional connectivity between the salience network, lingual gyrus and the occipital cortex during a ruminative state. Furthermore, the decoupling in salience network connectivity was associated with improvements in the ability to i) listen to the body for insight; ii) take a decentered perspective on one's experiences and iii) notice and let go of distressing thoughts and images, and mediated iv) the ability to sustain and control attention to bodily sensations. These psychological processes in turn predicted improved clinical outcomes. Hence, salience network connectivity during rumination may relate to key psychological processes underlying clinical improvement following MBCT treatment.

INTRODUCTION

Depression is a leading cause of disability worldwide; with global prevalence on the rise and the coronavirus pandemic threatening to unleash a wave of new cases (Hoare, Callaly, & Berk, 2020; 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 (Kupfer et al., 1992; Richards, 2011). 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, 2013a; Z. V. 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 (National Institute for Health and Care Excellence, October 2009, updated April 2018). MBCT trains adaptive attention regulation and present moment embodied awareness, and teach individuals with recurrent depression tools to recognize, decenter 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 can more easily be seen for what they are: overly negative predictions based on past experience rather than an objective reality.

Current research on the mechanisms by which MBCT treatment reduces depressive symptoms and relapse risk has focused mainly on self-reported psychological dispositions. Little is known about how MBCT impact neurocognitive functioning and states of depressive rumination (van der Velden et al., 2015). Recent reviews have called for triangulation across methods and incorporation of neuroscience to understand the key mechanisms (Davidson, 2016; Y. Y. Tang et al., 2015; van der Velden et al., 2015; van der Velden & Roepstorff, 2015; Vignaud et al., 2018; Young et al., 2018), and it is widely believed that the study of concurrent psychological and neurobiological processes holds great potential to enhance our understanding of mechanisms of change (Goodwin et al., 2018; Holmes et al., 2018).

The research on the neural correlates of mindfulness training ((Y. Y. Tang et al., 2015; Young et al., 2018) for reviews) and neural correlates of psychotherapeutic treatment for depression has grown exponentially the last decade (See (Marwood et al., 2018) for review). Broadly speaking, various forms of mindfulness-based interventions and practices have been found to alter brain function in neural regions and circuits that underlie attention, interoception, emotion regulation, and self-relevant processing (for reviews see (Gotink et al., 2016; Y. Y. Tang et al., 2015; Vignaud et al., 2018; Young et al., 2018)). However, research specifically on the the neural correlates of MBCT for recurrent depression (Vignaud et al., 2018; K. Williams et al., 2020) is still scarce.

A core skill by which MBCT is proposed to work in the treatment of recurrent depression, is teaching individuals with recurrent depression to recognize, decenter and decouple from conditioned patterns of depressive rumination by shifting the attention to the present-moment embodied experience. Hence, we choose to focus on neural networks related to depressive rumination and interoceptive awareness for our a priori analysis. We specifically chose a network-based functional connectivity approach, because network-based approaches have may hold particular promise in understanding the dynamics of complex mind states (Adele M. Hayes & Andrews, 2020; A. M. Hayes et al., 2015). The salience network, comprising of the anterior insula and the anterior cingulate cortex is involved with

interoceptive awareness, attention and emotion regulation (Downar et al., 2016), and is considered to be a neural hub regulating interactions between the control and self-processing systems, and facilitating adaptive regulation and integration of emotion, attention, and sensory experiences (Downar et al., 2016; Wang et al., 2016). The anterior insula of the salience network is has consistently been found to change in response to mindfulness interventions in both non-clinical and clinical populations (N. A. Farb et al., 2010; N. A. Farb et al., 2013; McGrath et al., 2013; Y.-Y. Tang & Leve, 2016; Y. Y. Tang et al., 2015; Wang et al., 2019; Young et al., 2018), and the anterior cingulate cortex of the salience network is one of the most commonly identified predictors of treatment response to psychotherapy in depression (Dutta et al., 2019; Godlewska et al., 2018; Lythe et al., 2015; Marwood et al., 2018). In contrast, the default mode network, comprising of the medial prefrontal cortex, posterior cingulate cortex/precuneus and angular gyrus is associated with self-related processing across a broad range of cognitive patterns (Murphy et al., 2019). In those at risk for depression, abnormal default mode connectivity repeatedly been implicated in persistent ruminative processing (Berman et al., 2014; Borders, 2020; Dichter et al., 2015; N. A. Farb et al., 2011; Feurer et al., 2021; J. P. Hamilton et al., 2015; Leech & Smallwood, 2019; Lydon-Staley et al., 2019; Marchetti et al., 2016; Smallwood et al., 2016; Wang et al., 2016; Wise et al., 2017), and default mode network connectivity has been advocated as promising target for MBCT for recurrent depression (Thorsten Barnhofer et al., 2016). Furthermore, depressive rumination is hypothesized to reflect a hyperactivation within and between the default mode network and the salience network, which together may been implicated in the negative valence, bias and self-referential processing characteristic of depressive rumination (Borders, 2020). Moreover, the salience network and default mode network tend to interact with other networks and regions that play a role in depression such as the central executive network and subcortical regions like the amygdala, hippocampus and striatum involved in abnormalities in sustained attention, working memory, memory, emotions and reward perception in depression (Borders (Borders, 2020) for review). Hence, to optimize statistical power to run primary analyses corrected for multiple comparisons, we constrained the 'a priori' neural networks examined in this study, to the default mode network and salience network, which we used as seeds and compared to the whole brain. Yet, given the novelty of the study, we also ran secondary explorative whole-brain analyses.

Here we present the first randomized controlled 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.

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 and 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).

Participants were recruited from general practices and local psychiatric units in the central region 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 behavior, 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 Regional Ethics Council in Central Denmark 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 Trials (Schulz, Altman, & Moher, 2010) and COBIDAS guidelines from the Organization for Human Brain Mapping's 'Statement on Neuroimaging Research and Data Integrity' (Nichols, 2016)

Randomization 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 (A. T. Beck et al., 1996) of less than 13 being asymptomatic, and greater than or equal to 14 being symptomatic. Research assessors conducting clinical interviews and magnetic resonance imaging (MRI) scans were masked to treatment allocation, and questionnaires were administered online. Patients were masked to treatment allocation at baseline assessment, but given the nature of psychological treatment, patients, clinicians and the trial coordinator were made aware of treatment allocation after baseline assessment.

Intervention

MBCT

MBCT is a manualized group-based program aiming to teach participants skills to prevent relapse or recurrence of depression (Segal et al., 2013b). MBCT integrates psychoeducational 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 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.

MEASURES AND PROCEDURES

Questionnaires

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, and three months follow up.

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

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

Mindfulness skills: We measured mindfulness skills at baseline and within a month after treatment using the 15-item version of the Five Factor Mindfulness Questionnaire, FFMQ (R. A. Baer et al., 2008; Gu et al., 2016).

Rumination: We measured trait rumination at baseline and within a month after treatment using the Rumination Response Scale (Roelofs et al., 2006)

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).

Given the lack of studies of MBCT and neural connectivity and similar paradigms, we had insufficient information to perform a power calculation. Instead, we based the power estimate on Mumford and colleagues guidelines suggesting 30 per group in fMRI neuroimaging for medium to small effects (Mumford, 2012) and Poldrack and colleagues guidelines (Poldrack et al., 2017) on 'transparent and reproducible neuroimaging research', the latter which used the neurosynth database to estimate average fMRI power, suggesting 28.5 per group for a medium to large effect. On this basis by having 50 in the MBCT group and 30 in the control group, we estimated we could find a medium - large effect size, allowing for 20% attrition in the MBCT group (Poldrack et al., 2017).

fMRI paradigm

The fMRI 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. We chose this particular order for the states for the following reasons: i) We wanted to start with a resting state to assess general vulnerability; ii) The resting state after mindfulness was to allow us to can address the consequence of the brief mindfulness practice on resting state, and to create a gap before the rumination state; iii) The rumination state was last as

it was deemed most likely to have a 'spill over' effect on the other states. We deliberately did not counterbalance the order of the states (e.g. randomize them) as we wanted to compare the same state before and after treatment, hence by keeping the order fixed. Any effect of order such as tiredness would be similar before and after treatment, whereas differential effects would be likely an impact of treatment allocation. Given cardiorespiratory differences between states (see supplements), and the known effect of cardiorespiratory interference with signal-to-noise ratios (Cordes, Nandy, Schafer, & Wager, 2014; S. Smith & Beckmann, 2017)we decided to only compare the same states to each other and not across states (i.e. pre vs post resting state; pre vs post mindfulness practice, pre vs post resting state 2 and pre versus post 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 and colleagues (Martinon, Smallwood, McGann, Hamilton, & Riby, 2019; 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 supplements S1 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 et al., 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., 2013b). 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 their attention to the sensation of the breath and, finally, to expand their 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.

MRI ACQUISITION AND PREPROCESSING

MRI acquisition

Functional and structural images of the brain were acquired on a 3 Tesla Siemens Magneton Skyra 3T scanner (Siemens, Erlangen, Germany, software version Scout) using a 32-channel head coil. A structural three dimensional T1-weighted (3D-T1) scan was acquired with the following parameters:

176 slices covering the whole brain, TE (echo time)/TR(repetition time) = 3.8/2300 ms, inversion time = 31260 ms, flip angle = 8°, Field of View (FOV) = 256 mm, spatial resolution 1 × 1 × 1 mm^3, Generalized Autocalibrating Partially Parallel Acquisitions (Grappa) = 2, and phase-encoding direction = AP.

Resting state, mindfulness and rumination state fMRI

Four fMRI scans of each five minutes duration were acquired to evaluate how states of rest, mindfulness, and rumination affect functional connectivity with a second resting state between the mindfulness and rumination state. For each state 203 volumes of 2D gradient-echo EPI fMRI data were acquired with the following parameters: 52 ascending axial slices covering the whole brain, 3.8 × 3.8 × 3.8 mm^3, FOV 192, Grappa = 2, Multiband = 2, TE/TR = 30/1480 ms, flip angle = 65°, and phase-encoding direction = AP.

FMRI preprocessing

We used FSL tools (S. M. Smith et al., 2004) for preprocessing. Preprocessing steps followed standard procedures and included: skull-stripping (BET tool (S. M. 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).

ANALYSES

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. Voxels were kept in their original space for analysis.

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 (ITT), 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.

Mechanisms analyses

To look at mechanisms and compare neural findings with psychological process findings, we needed analyses using only complete cases as change can only be evaluated in these cases.

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.

For completeness, we also report explorative results that were significant across all Yeo networks and selected seeds when not using correction for multiple comparisons (see S4 in supplements).

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

We correlated change in neural connectivity with change in self-report measures using Pearson's r correlations across change scores. For significant correlations we also ran a mediation analysis to test whether the effect of treatment on change in neural connectivity was mediated by change in self-report measures, or whether change in self-report measures were mediated by change in neural connectivity using Hayes Process Macro version 2 model 4 in SPSS based on the principles of ordinary least squares regression with bias-corrected bootstrapping (A. F. Hayes & Rockwood, 2017) using 5.000 iterations and 95% confidence intervals.

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 here we obtained pre and post treatment FMRI scans from 28 participants in the MBCT group and 20 participants in the TAU group).

Descriptive baseline data is shown in Table 1. No baseline groups differences were found for any sociodemographic variables, clinical characteristics, or outcome measures. Of the 8 sessions, the mean attendance was 6.75 sessions with 94% attending at least 4 sessions. Those not participating in the rumination condition (N = 20) had higher symptoms at baseline, but did not differ on other measures (see supplements) and hence the finding on the rumination state may mainly refer to those with no residual symptoms to mild symptoms.

Clinical and psychological change processes

Clinical and psychological change process results have been reported in full elsewhere (van der Velden et al., in prep). In brief, amongst individuals with recurrent depression in remission or with mild to moderate residual symptoms, MBCT treatment significantly reduced depressive symptoms (g=0.82, p= 0.001) compared with the TAU group at post treatment, and at 3 months follow up (g=0.51 p=0.002). Mean attendance to MBCT was 6.75 out of 8 sessions with (N=45, 93.88 %) of the MBCT group attending at least 4 sessions. Compared with the TAU control group, individuals with recurrent depression receiving MBCT reported increased decentering (EQ) (p<.001, g=0.98, 95% CI [3.76, 11.01]), mindfulness (FFMQ) (p<.001, g= 0.68, 95% CI [1.49, 9.57]), 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) or for the tendency not to ignore or distract oneself from sensations of pain or discomfort (MAIA - not distracting subscale) (see supplements for complete results). Of these, increases in decentering, dispositional mindfulness, active listening to the body for insight and the ability to sustain and control attention to body sensations all predicted depressive symptoms at 3 months follow up (see table 2).

	MBCT+TAU (N=50)	TAU (N=30)
Sociodemographic characteristics	N=48	N=28
Age	43.17 (14.22)	45.25 (12.01)
Gender (Female/Male)	35/15 (70%)	23/5 (82%)
Educational level		
Low (<2 years further education)	15 (30%)	3 (11%)
Medium (2-4 years further education)	24 (48%)	21 (75%)
High (>5 years further education)	9 (18%)	4 (14%)
Marital status		
Married/cohabiting	43 (90%)	21 (75%)
Single/not cohabiting	5 (10%)	7 (25%)
Occupational status		
Employed	24 (50%)	14 (50%)
Unemployed/benefits	10 (10%)	4 (14%)
Student	3 (6%)	1 (4%)
Retired	7 (15%)	4 (14%)
Other	9 (19%)	5 (18%)
Clinical Characteristics	N=50	N=28
Symptomatic (QIDS>5)	43 (83%)	25 (76%)
Antidepressant usage	43/7 (86%)	21/7 (75%)
Childhood Trauma	58.79 (6.22) N=42	58.96 (6.33) N=26
Previous episodes of depression	3.90 (1.44) N=41	3.80 (1.36) N=23
Outcomes	N=48	N=27
QIDS	9.23 (4.58)	9.68 (5.10)
EQ	31.43 (7.12)	31.26 (7.06)
MAIA_AR	17.22 (5.03)	17.78 (4.99)
MAIA_BL	6.25 (2.07)	7.40 (3.25)
MAIA_TR	8.89 (3.31)	8.40 (3.77)
MAIA_NO	12.79 (2.61)	13.96 (3.38)
MAIA_ND	9.17 (2.64)	9.01 (2.45)
MAIA_EA	15.32 (3.51)	16.57 (4.23)
FFMQ	44.21 (8.88)	45.33 (80.2)
RRS	53.38 (9.80)	57.51 (8.24)

Table 1: Baseline characteristics: QIDS: Quick Inventory of Depressive Symptomology (Rush et al., 2003); EQ: Experience Questionnaire(Fresco, Moore, et al., 2007); FFMQ: Five Factor Mindfulness Questionnaire(R. A. Baer et al., 2008); RRS: Rumination Response Scale(Roelofs et al., 2006); MAIA (Multidimensional Assessment of Interoceptive Awareness(Mehling et al., 2012) and the subscales of AR: Attention Regulation; BL: Body listening; NO: Noticing; TR: Trusting; ND: Non distracting; EA: Emotional awareness

Figure 1: Participant Flow

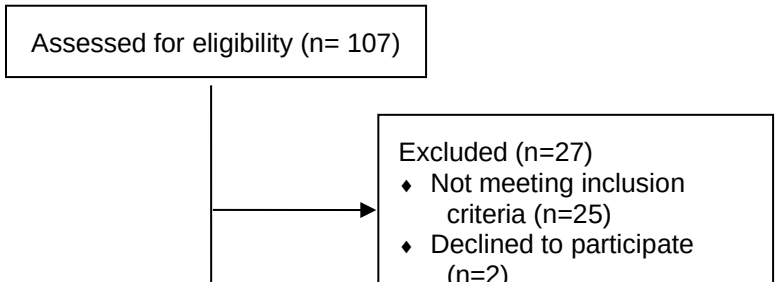

Table 2: Prediction of clinical outcomes

Change in mechanisms predicting clinical outcomes at three months follow up

	Unstandardized	Coefficients	Standardized Coefficients			95% Confidence Interval for B	
Model	B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
EQ	-.261	.065	-.456	-4.002	.000	-.391	-.130
FFMQ	-.265	.061	-.484	-4.324	.000	-.387	-.142
MAIA_AR	-.267	.102	-.319	-2.625	.011	-.471	-.064
MAIA_BL	-.634	.216	-.352	-2.938	.005	-1.066	-.203
MAIA_EA	-.228	.123	-.231	-1.856	.068	-.473	.018
MAIA_NO	-.104	.166	-.080	-.624	.535	-.436	.229

Table 2: Change in psychological mechanisms predicting change in depressive symptoms at three months (QIDS3 minus QIDS1) follow up. EQ: Experience Questionnaire(Fresco, Moore, et al., 2007); FFMQ: Five Factor Mindfulness Questionnaire(R. A. Baer et al., 2008); RRS: Rumination Response Scale(Roelofs et al., 2006); MAIA (Multidimensional Assessment of Interoceptive Awareness(Mehling et al., 2012) and the subscales of AR: Attention Regulation; BL: Body listening; NO: Noticing; TR: Trusting; ND: Non distracting; EA: Emotional awareness. Only significant group x time effects were tested.

Neural results

Manipulation check of fMRI paradigm

The study design was tailored to address how MBCT can affect general vulnerability i.e. resting state, a state of mindfulness practice and a state of depressive rumination. The rumination state was designed to trigger a situation of vulnerability that were likely to induce ruminative negative thought patterns. (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 (see method section for more details)). The mindfulness state on the other hand was designed to induce awareness of present-moment embodied experiences. 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 supplements). As expected, rumination strongly increased negative self-related thoughts and decreased body awareness compared to all other conditions (figure 2A, all $p<0.01$). In contrast, mindfulness induction led to fewer negative self-related thoughts and increased body awareness compared to both resting state and the rumination state.

Figure 2: Change in experience sampling after each state

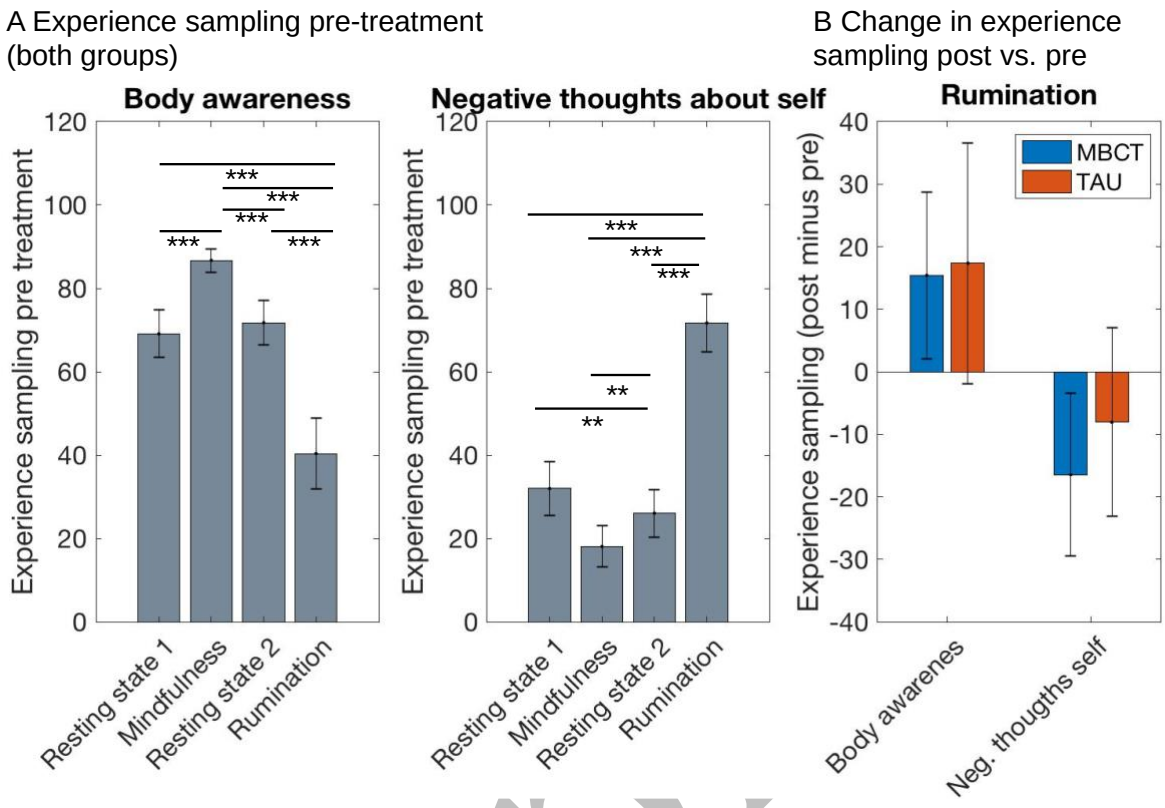

Figure 2. Experience sampling after each scan. A) Experience sampling pretreatment (both groups combined). The different scan conditions affected the responses to the experience sampling. After the rumination scan, participants reported less body awareness and more negative thoughts about themselves than after either rest or mindfulness. Error bars show 95% confidence intervals. *p<0.05, **p<0.01, ***p<0.001, significance stars show in (A): within subject t-tests comparing the different scan conditions; in (B) t-tests comparing the groups.

Change in neural connectivity as function of treatment

To examine whether treatment changed neural connectivity between either the default mode or salience network 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 (P>0.0125) 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 2A).

Furthermore, we found that the groups did not differ pre treatment (occipital: Mann-Whitney U=396, p=0.19, rank biserial correlation=0.2, lingual gyrus: Mann-Whitney U=374, p=0.374, rank biserial correlation=0.149). Instead, the MBCT group showed 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 (S3) for other scan conditions.

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 (see supplements). These showed that salience network to lingual gyrus was significantly correlated with change with: the ability to sustain and control attention to body sensations (MAIA_attention regulation r=-0.657, P>0.000); active listening to the body for insight (MAIA_body listening subscale r=0.503, p=0.001); MAIA_noticing (r=-0.460, p=0.002); decentering (r=-0.452, p=0.002), and non-reactivity to inner experiences (FFMQ_non reactivity r=-0.342, p=0.023). For the salience network to occipital cortex was correlated with the ability to sustain and control attention to body sensations (MAIA_attention regulation r=-0.333, P>0.027); active listening to the body for insight (MAIA_body listening subscale r=-0.366, p=0.015).

Furthermore, the decoupling of the salience network to the lingual gyrus mediated increases in the ability to sustain and control attention to body sensations (indirect effect B-3.46, BSCI [-6.70 to - 1.02]), explaining 57% of the effect. Although the neural change in connectivity during rumination and psychological changes were concurrent, and hence the question of directionality unclear, the changes (i.e. change in ability to sustain and control attention to body sensations; active listening to the body for insight; decentering and non-reactivity) predicted clinical outcomes post treatment and at 3 months follow up (van der Velden et al., in prep, paper 5).

Furthermore, explorative comparisons across all 17 Yeo networks and subcortical seeds of amygdala, hippocampus and striatum, related to the whole brain, identified a change in amygdala linked to similar visual areas and a change in somato-motor network linked to cerebellum during rumination (see supplements). For these analyses we only applied threshold-free cluster enhancement (TFCE), but did not further correct for multiple comparisons across number of networks and seeds given the exploratory nature of these analyses.

Figure 3: Change in neural connectivity as a function of treatment

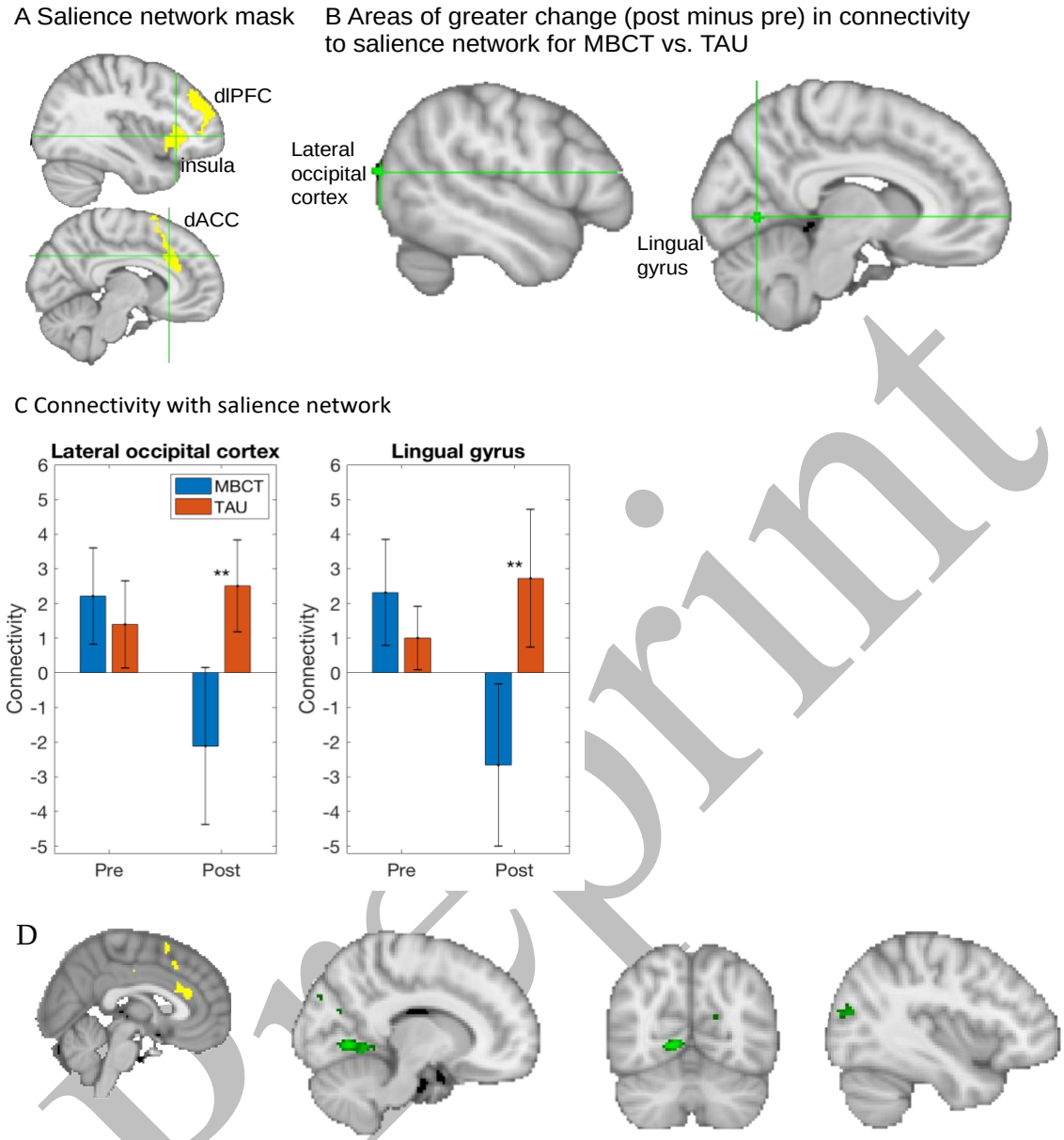

Figure 3. Change in neural connectivity as a function of treatment. A) The mask for the salience network included the dorsal anterior cingulate cortex, the dorsolateral prefrontal cortex and the anterior insula. B) Comparing the effect of MBCT vs. TAU on change in connectivity (post minus pre MBCT/TAU) with salience network . Connectivity is changed to the lateral occipital cortex and the lingual. C) Connectivity between salience network 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 salience network compared to TAU post treatment while there was no difference between the groups pre-treatment. D) Uncorrected findings p>0.05. Error bars show 95% confidence intervals. *p<0.05, **p<0.01 for two-tailed t-tests comparing the two groups.

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.

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, have been found to predict treatment response across various forms of psychotherapy for depression (Marwood et al., 2018), change in response to mindfulness-based interventions across clinical and nonclinical populations (Y. Y. Tang et al., 2015; Young et al., 2018), and those showing reduced depressive symptoms (N. A. Farb et al., 2010), and play a key role in the negative bias, valence, and persistence of depressive rumination (Borders, 2020). The lingual gyrus is a multimodal association cortex associated with amongst others multisensory integration, working memory ((Froudarakis et al., 2019; Le, Borghi, Kujawa, Klein, & Leung, 2017)), declarative memory (van der Werff et al., 2013), self-criticism (Kim, Kent, Cunnington, Gilbert, & Kirby, 2020) and episodic memory and emotional processing during depression (Kukolja, Goreci, Onur, Riedl, & Fink, 2016). The lingual gyrus to salience network connectivity has been related to depression ((Liu et al., 2017)), and resilience to develop psychopathology (van der Werff et al., 2013) and depression (Chang et al., 2017). The occipital cortex has been associated with visualization of painful experiences, memory retrieval, and emotional processing during depression (Teng et al., 2018). While the uncoupling in salience network connectivity to lingual gyrus and visual areas did not relate to change in experience of negative self-related thoughts or body awareness during the rumination induction, it may relate to how likely participants are to get stuck in persistent ruminative processing after the rumination induction, as this neural uncoupling was associated with improvements in the ability to i) listen to the body for insight; ii) take a decentered perspective on one's experiences and iii) notice and let go of distressing thoughts and images, and mediated iv) the ability to sustain and control attention to bodily sensations. These changes in psychological dispositions further predicted clinical outcomes post treatment and at 3 months follow up. Thus, salience network connectivity during rumination may relate to key psychological processes underlying clinical improvement following MBCT treatment.

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 et al., 2013b). The lack of change found in ruminative dispositions scores and default mode network 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. (J. P. Hamilton et al., 2015; Wang et al., 2016). Although it is also possible that we were not powered to detect smaller effects of change in default mode network.

In addition to the 'a priori' analysis of the salience network and default mode network seed of interest, we also conducted preplanned explorative analyses across all 17 yeo networks and subcortical regions (i.e. amygdala, hippocampus and striatum) (see appendix 4) . These analyses showed a change in amygdala to lingual gurys, and the somatomotor network (to cerebellum) during rumination. The amygdala is often viewed as an extension of the salience network and play a role in emotional processing during depression (Borders, 2020). Both the amygdala and sensory areas of the somatomotor network have been related to change in response to mindfulness training (Y. Y. Tang et al., 2015), however, this is the first time a study has identified a change in these regions during a ruminative state in response to MBCT treatment. Hence, future research may want to investigate these regions 'a priory' and future determine how change in these regions related to psychological constructs and clinical outcomes.

The study has a number of methodological strengths. First, the study design was tailored to address how MBCT can affect general vulnerability i.e. resting state, a state of mindfulness practice, and a state in depressive rumination is induced, and the RCT design allowed us to evaluate the impact of MBCT treatment on neural connectivity. 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; Y. Y. 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. First, due to the novelty of the design, it was difficult to make precise statistical power estimations. We arranged our power estimation on basis of the guidelines by Mumford and colleagues (2012) and Poldrack and colleagues (Poldrack, 2019) suggesting around 30 per group for a medium to large effect. This estimation, however, did not consider the power needed for the other measures. Also, both fMRI estimations are based on contrasting across different task, states or groups, and power estimations may not be fully applicable when comparing the same individuals entering the same states before and after treatment, with the only difference being the treatment allocation. Hence, the study may be underpowered for mediation analyses of small - medium effects, but also small to medium fMRI effects. Thus, for null effects we cannot preclude a lack of mechanistic relevance. Second, we chose only to compare the same states as a function of treatment and time, and did not compare the states against each other, as the states differed substantially on cardiorespiratory levels (see supplements, which is known impact signal to noise ratios and complicates comparisons. Third, we chose treatment as usual as control group, as we wanted to know how the intervention of MBCT as a whole affects neural change, and whether such neural change predicts 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. Furthermore, we were not able to identify a direct predictive relationship between the neural effects and concurrent or prospective depression outcomes, but an indirect relationship, where neural change mediated change in psychological processes, which in turn predicted proximal and distal clinical outcomes. Out of ethical reasons, participants could opt out of the rumination condition, meaning that the neural findings can only be generalizable to participants

willing to participate in the rumination induction. Those not participating in the rumination condition had higher symptoms at baseline, but did not differ on other measures and hence the finding on the rumination state may mainly refer to those with no residual symptoms to mild symptoms.

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 completing the rumination condition. Shifting the focus of future research to mind states characterized by high vulnerability 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 (MBCT) compared with treatment as usual led to decreased functional connectivity between salience network connectivity and lingual gyrus and occipital cortex during a ruminative state. Furthermore, the decoupling in salience network connectivity was correlated with the ability to listen to bodily sensations, take decentered perspective and notice, step back and let go of distressing thoughts and images, and mediated change in the ability to sustain and control attention to bodily sensations, explaining 57% of the effect. These psychological processes in turn predicted improved clinical outcomes. As such, salience network connectivity during rumination may relate to key psychological processes underlying clinical improvement following MBCT treatment.

Data sharing statement and trial registration

Deidentified individual participant data that underlie the results reported in this article, is available upon request to researchers with a methodological sound proposal. Proposals should be directed to the corresponding author. Group data, study protocol and analytical code will be made available for download on Github. The study was registered at ClinicalTrials.gov (NCT03353493).

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Contributors

AMV, AR and WK were responsible for the original proposal and AMV secured funding for the trial. AMV developed the design and protocol, and AR, WK, JSmallwood, CJH, SWL advised on the design. AMV was responsible for the general management of the study and LOF oversaw the clinical management of the study. AMV, EE and LOF collected the data. JSmallwood, JScholl, AMV, AR and

WK created the analysis strategy. JScholl analysed the MRI data, and JScholl and MSO analysed the self-report data and clinical data. JScholl, AMV, JSmallwood, SWL, CJH, MSO, AR and WK interpreted the data. JScholl and AMV wrote the initial draft of the methods and results, and AMV wrote the initial draft of the introduction and discussion. All authors contributed to, and approved, the final manuscript.

Conflicts of interest

The author(s) declares the following potential conflicts of interest. WK is the director of the Oxford Mindfulness Centre. He receives payments for training workshops and presentations related to MBCT and donates all such payments to the Oxford Mindfulness Foundation, a charitable trust that supports the work of the Oxford Mindfulness Centre. WK was until 2015 an unpaid Director of the Mindfulness Network Community Interest Company and gave evidence to the UK Mindfulness All Party Parliamentary Group. He received royalties for several books on mindfulness published by Guilford Press. LOF is director of the Danish Centre for Mindfulness. She receives payments for presentations, workshops and teacher training related to MBSR and MBCT and donates payments to the Danish Centre for Mindfulness.

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SUPPLEMENTS

S1: Experience sampling questions

Component and questions	Resting state I+II	Mindfulness state	Rumination state
1.Manipulation check			
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			
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			
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**		

Table S1. Experience sampling questions after each state. Participants were asked to rate their agreement to each question in the three components on a 0-100% VAS scale (See methods for detailed description of the paradigm).

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

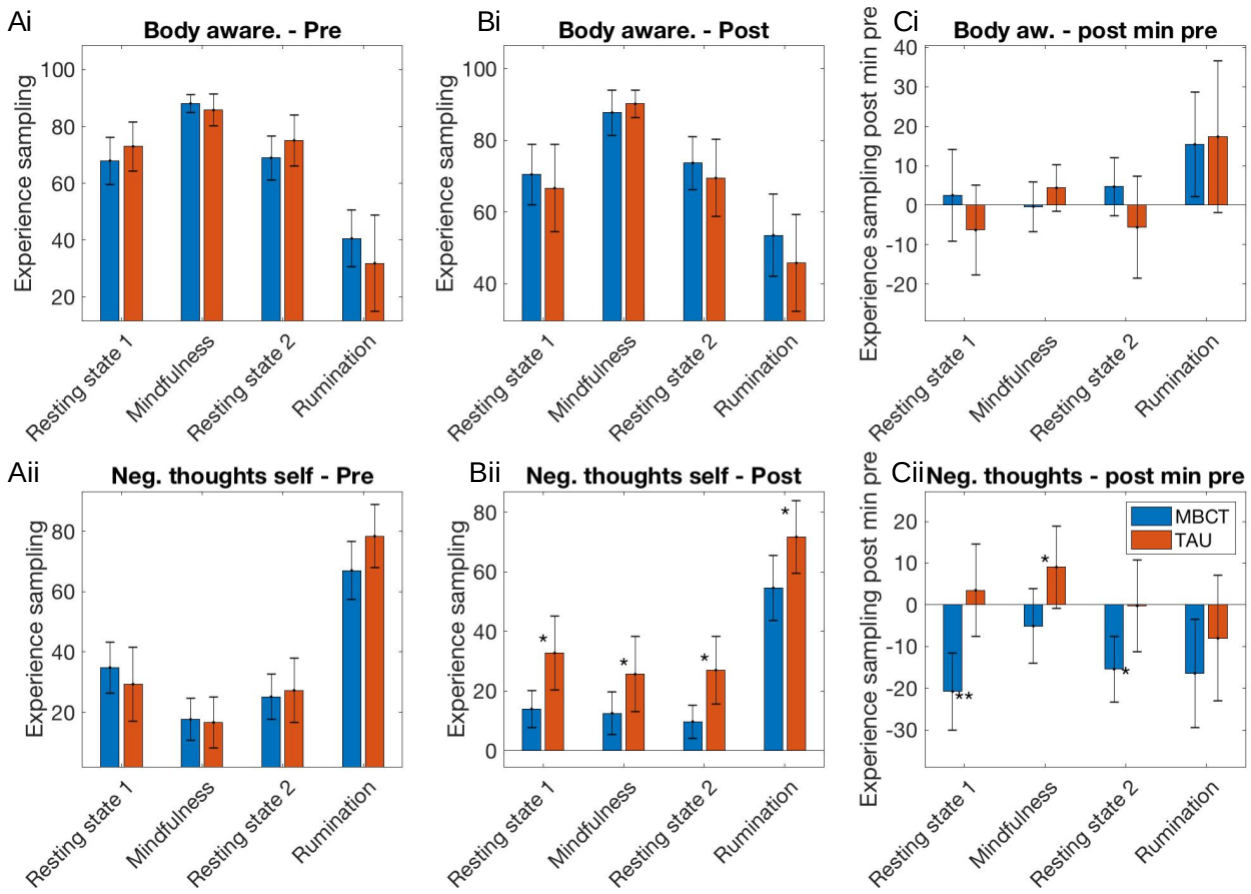
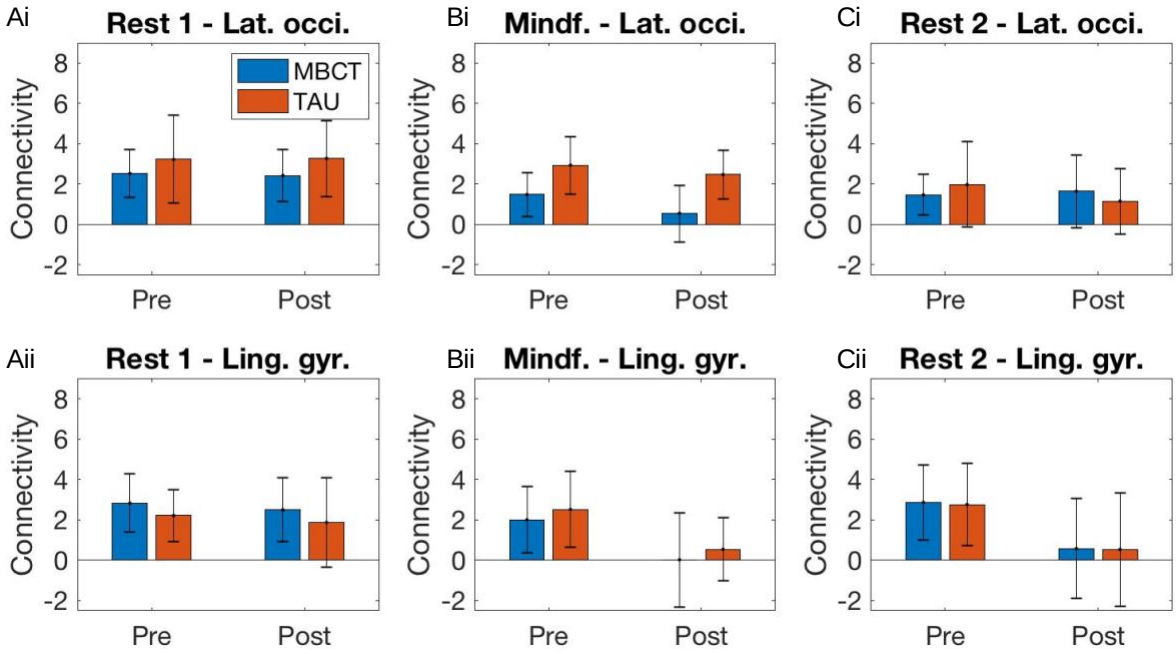


Figure S2. Pre-post experience sampling reports after each state. A: Pre-treatment, MBCT (blue) and TAU (red) groups do not differ in any post-scan self reports. B: Post-treatment, MBCT groups shows reduced negative thoughts about self in each scan, but not changes to body awareness. C: Comparison of 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 resting state 1, mindfulness and resting state 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 resting state 1 (rest 1) (A), mindfulness (B) and resting state 2 (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).

S4: Exploratory neural connectivity during across all Yeo networks and whole brain connectivity:

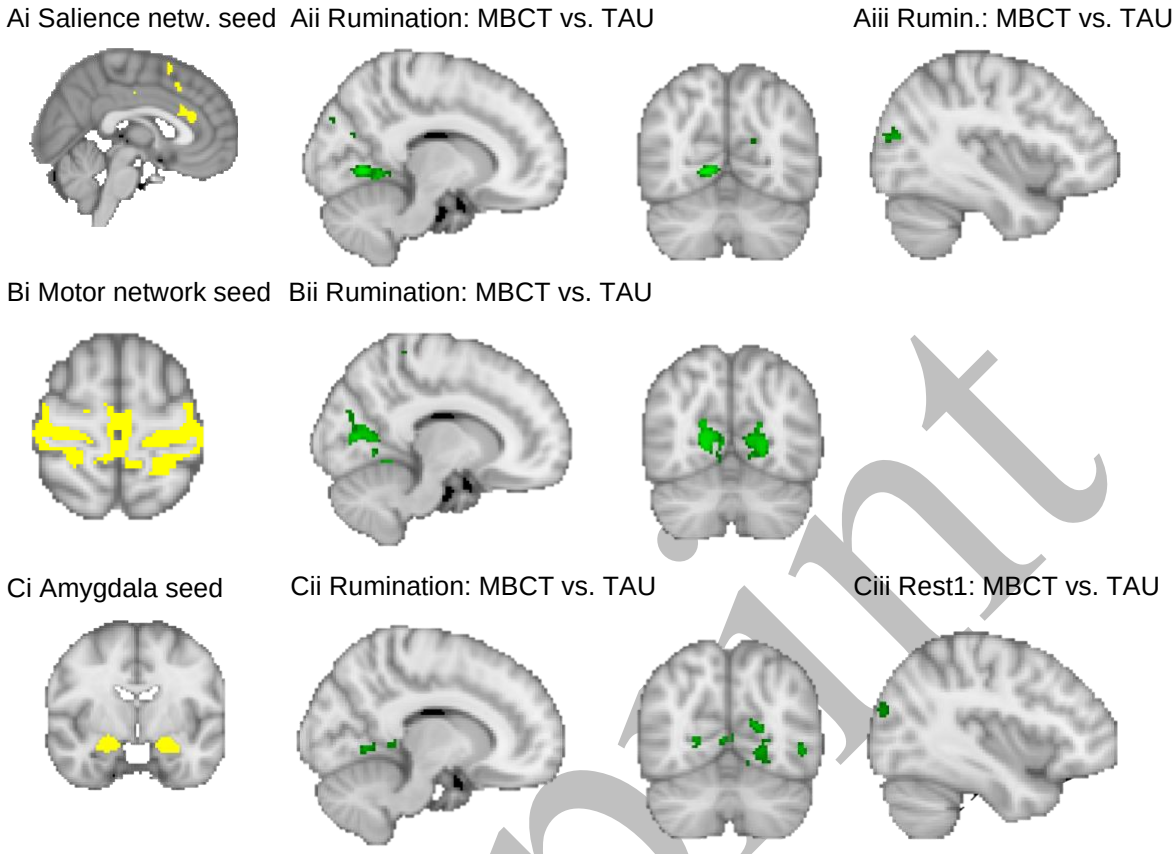


Figure S4. Connectivity change (post minus pre) in the two groups (MBCT vs. TAU). For completeness, the effect of treatment was also tested using the other Yeo networks, as well as subcortical areas (amygdala, hippocampus, ventral striatum) as seeds. Given the explorative nature of these results, we did not correct for multiple comparisons across seeds, but only for two-tailed tests within each network ($p<0.05$, cluster corrected, see methods). The seeds for which there were significant effects of treatment were: A) Salience network (as in main text, but different threshold [corrected only for one network rather than two] used here for comparison) – showing difference in connectivity (MBCT vs. TAU, post vs. pre) during rumination to visual cortical areas (Ai+ii). B) Motor network – differences in connectivity to similar visual areas during rumination (Bii). C) Amygdala – differences in connectivity during rumination (Cii) and first resting state (i.e. before the mindfulness scan, Ciii) to lingual gyrus and similar visual cortical areas. However, note that the visual Yeo network overlapping with these areas as seed did not reveal any significant group differences.

S5: Correlations between neural effects and psychological processes predicting clinical outcome

Correlations

		EQ	FFMQ	MAIA_BL	MAIA_AR	SN_LO	SN_RL
EQ	Pearson Correlation	1	.744**	.665**	.669**	.257	.452**
	Sig. (2-tailed)		.000	.000	.000	.092	.002
	N	66	66	66	66	44	44
FFMQ	Pearson Correlation	.744**	1	.429**	.684**	.131	.266
	Sig. (2-tailed)	.000		.000	.000	.397	.081
	N	66	66	66	66	44	44
MAIA_BL	Pearson Correlation	.665**	.429**	1	.625**	.366*	.503**
	Sig. (2-tailed)	.000	.000		.000	.015	.001
	N	66	66	66	66	44	44
MAIA_AR	Pearson Correlation	.669**	.684**	.625**	1	.333*	.657**
	Sig. (2-tailed)	.000	.000	.000		.027	.000
	N	66	66	66	66	44	44
SN_LO	Pearson Correlation	.257	.131	.366*	.333*	1	.537**
	Sig. (2-tailed)	.092	.397	.015	.027		.000
	N	44	44	44	44	48	48
SN_RL	Pearson Correlation	.452**	.266	.503**	.657**	.537**	1
	Sig. (2-tailed)	.002	.081	.001	.000	.000	
	N	44	44	44	44	48	48

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Abbreviations: QIDS: Quick Inventory of Depressive Symptomology (Rush et al., 2003); EQ: Experience Questionnaire(Fresco, Moore, et al., 2007); FFMQ: Five Factor Mindfulness Questionnaire(R. A. Baer et al., 2008); RRS: Rumination Response Scale(Roelofs et al., 2006); MAIA (Multidimensional Assessment of Interoceptive Awareness(Mehling et al., 2012), and the subscales of AR: Attention Regulation; BL: Body listening. SN_RL: Salience network connectivity to right lingual gyrus, SN_LO: Salience network connectivity to left occipital cortex.

S6: Sample characteristics of those not participating in the rumination condition

One way ANOVA based on rumination state participation

		Sum of Squares	df	Mean Square	F	Sig.
FFMQ_change	Between Groups	74.145	1	74.145	1.060	.307
	Within Groups	4478.173	64	69.971		
	Total	4552.318	65			
EQ_change	Between Groups	10.237	1	10.237	.155	.695
	Within Groups	4233.650	64	66.151		
	Total	4243.887	65			
RRS_change	Between Groups	119.667	1	119.667	1.020	.316
	Within Groups	7506.469	64	117.289		
	Total	7626.137	65			
MAIA.NO_change	Between Groups	1.898	1	1.898	.151	.699
	Within Groups	803.633	64	12.557		
	Total	805.530	65			
MAIA.ND_change	Between Groups	.346	1	.346	.040	.842
	Within Groups	555.472	64	8.679		
	Total	555.818	65			
MAIA.EA_change	Between Groups	10.691	1	10.691	.434	.512
	Within Groups	1575.441	64	24.616		
	Total	1586.132	65			
MAIA_AR_change	Between Groups	3.270	1	3.270	.110	.741
	Within Groups	1899.215	64	29.675		
	Total	1902.485	65			
MAIA_BL_change	Between Groups	7.151	1	7.151	1.086	.301
	Within Groups	421.349	64	6.584		
	Total	428.500	65			
QIDS_change*	Between Groups	186.708	1	186.708	7.522	.008
	Within Groups	1712.616	69	24.821		
	Total	1899.324	70			

Comparing those who participated in the rumination condition (n=68) versus those who did not (n=20) on mechanism measures and depressive symptoms. Differences between QIDS were driven by higher depressive symptoms at baseline amongst those opting out of ruination, whereas post treatment results on depressive symptoms were similar. QIDS: Quick Inventory of Depressive Symptomology (Rush et al., 2003); EQ: Experience Questionnaire(Fresco, Moore, et al., 2007); FFMQ: Five Factor Mindfulness Questionnaire(R. A. Baer et al., 2008); RRS: Rumination Response Scale(Roelofs et al., 2006); MAIA (Multidimensional Assessment of Interoceptive Awareness(Mehling et al., 2012), and the subscales of AR: Attention Regulation; BL: Body listening; NO: Noticing; TR: Trusting; ND: Non distracting; EA: Emotional awareness.

S7: Physiological and experience sampling change across state and treatment allocation