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# Archival Report

## Mindfulness Training Changes Brain Dynamics During Depressive Rumination: A Randomized Controlled Trial

Anne Maj van der Velden, Jacqueline Scholl, Else-Marie Elmholt, Lone O. Fjorback, Catherine J. Harmer, Sara W. Lazar, Mia S. O'Toole, Jonathan Smallwood, Andreas Roepstorff, and Willem Kuyken

### ABSTRACT

**BACKGROUND:** Depression is a leading cause of disability worldwide and its 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.

**METHODS:** In a randomized controlled functional magnetic resonance imaging study ( $N = 80$ ), we looked at the neurocognitive mechanisms behind mindfulness-based cognitive therapy ( $n = 50$ ) for recurrent depression compared with treatment as usual ( $n = 30$ ) across experimentally induced states of rest, mindfulness practice and rumination, and the relationship with dispositional psychological processes.

**RESULTS:** Mindfulness-based cognitive therapy compared with treatment as usual led to decreased salience network connectivity to the lingual gyrus during a ruminative state, and this change in salience network connectivity mediated improvements in the ability to sustain and control attention to body sensations.

**CONCLUSIONS:** These findings showed that a clinically effective mindfulness intervention modulates neurocognitive functioning during depressive rumination and the ability to sustain attention to the body.

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Depression is a leading cause of disability worldwide with its global prevalence on the rise (1,2). The risk of relapse increases with every episode of depression, and after 3 episodes the relapse rate can be as high as 80% (3,4). Recurrent depression is characterized by increased cognitive reactivity, in which changes in mood can easily activate negative biases and ruminative states. These states have been linked to the onset, maintenance and perpetuation of depressive symptoms and increased risk of relapse (5–8).

Mindfulness-based cognitive therapy (MBCT) is an effective treatment for the prevention of risk of relapse among individuals with a history of recurrent depression (9) and is recommended as a preventive treatment in a number of national health guidelines (10). MBCT trains individuals in adaptive attention regulation and present-moment embodied awareness as key therapeutic skills (6). This teaches individuals with recurrent depression to recognize and decouple themselves from rumination by shifting attention 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 (6). 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 objective reality. Such adaptive attention regulation is hypothesized to be a core skill which makes MBCT effective in preventing depressive relapse (6).

Current research on the mechanisms by which MBCT reduces depressive symptoms and relapse risk has focused mainly on self-reported psychological traits. The research on the neural correlates of mindfulness training (11,12) and psychotherapeutic treatment for depression has grown exponentially in the last decade (13). Generally 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 (11,12,14,15)]. However, research specifically on the neural correlates of MBCT for recurrent depression is still scarce (14,16).

A core skill taught to individuals with recurrent depression in MBCT treatment is to recognize, decenter, and decouple from conditioned patterns of depressive rumination by shifting attention to the present-moment embodied experience (6). Hence, we chose to focus on neural networks related to depressive rumination and interoceptive awareness for our a priori analysis using the network-based functional connectivity

approach (17,18). Two networks have received much attention in the context of the clinical neuroscience of depression and have been linked to depression vulnerability, rumination, and treatment response: the salience network (SN) and the default mode network (DMN) (13,19–24). The SN plays a central role in attention and emotion regulation as well as in integrating and filtering interoceptive, autonomic, and emotional information (25). The DMN is associated with a broad range of states, including social cognition, self-referential processes, and the inability to disengage from ruminative and negatively biased thought patterns during depression (22). Both networks have been implicated in depressive symptomatology and prediction of treatment response (13,26–28) and have been found to respond to mindfulness training in healthy participants (11,12,14,29–31). Moreover, the SN and DMN 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 (32). We constrained the a priori neural networks to the DMN and SN, which we used as seeds and compared with the whole brain; however, given the novelty of the study, we also ran secondary explorative whole-brain analyses.

Here we present a novel randomized controlled functional magnetic resonance imaging (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 in which mindfulness and rumination were induced, followed by experience sampling and questionnaires examining cognitive and affective experiences.

## METHODS AND MATERIALS

### Study Design and Participants

We set up a single-blind, randomized controlled trial examining neural mechanisms of change and concurrent psychological processes in MBCT+treatment as usual (TAU) and TAU alone. The study design was preregistered at [ClinicalTrials.gov](https://www.clinicaltrials.gov) (identifier: NCT03353493) and the Danish Data Protection Agency and was approved by the Regional Ethics Council.

Participants were recruited from general practices and local psychiatric units in the Central Jutland region of Denmark by 2 members of the research team (AMvdV and LF). Inclusion criteria were a diagnosis of recurrent major depressive disorder, with or without a current episode, established through the Structured Clinical Interview for DSM-IV-TR (33); 3 or more previous major depressive episodes; age 18 years or older; and, if on antidepressants, a stable dose of selective serotonin reuptake inhibitor or serotonin and norepinephrine reuptake inhibitor medication for a minimum of 8 weeks. Exclusion criteria were a current severe major depressive episode [Beck Depression Inventory-II > 28 (34)] or a history of schizophrenia, schizoaffective disorder, bipolar disorder, current severe substance abuse, organic mental disorder, current/past psychosis, pervasive developmental delay, persistent antisocial behavior, or persistent self-injury requiring clinical management/therapy; formal concurrent psychotherapy; having previously completed MBCT/mindfulness-based stress reduction training and/or

having extensive meditation experience (i.e., retreats or regular meditation practice); or antipsychotic medication and benzodiazepines. All participants gave written informed consent.

### Randomization and Masking

Participants ( $n = 80$ ) were randomly allocated (in a 5:3 ratio) to receive either an 8-week MBCT class+TAU or adhere to TAU. Patients were randomly assigned by an independent researcher to the 2 groups with a computer-generated random number sequence and stratified according to antidepressant use and participants' symptom status at randomization (Beck Depression Inventory-II) (34). Research assessors conducting clinical interviews and MRI scans were masked to treatment allocation, and patients were masked to treatment allocation at baseline assessment.

### Intervention and Procedures

MBCT is a manualized group-based program aiming to teach participants skills to prevent relapse or recurrence of depression (6). MBCT integrates psychoeducation elements from cognitive behavioral therapy for depression with systematic training in mindfulness meditation techniques from the mindfulness-based stress reduction program. MBCT consisted of a preclass interview and weekly classes of 2.25 hours during an 8-week period with homework and 4 booster sessions offered every 3 months after the program. Two experienced MBCT therapists fulfilling internationally recognized good practice guidelines for teachers, trainers, and supervisors of mindfulness courses (35) delivered 4 MBCT group sessions in university settings. We restricted TAU to no psychotherapeutic intervention and either a stable dose of antidepressant medication or no medication.

### Measures and Procedures

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

### Self-report Measures

Before and after treatment, we assessed depressive symptoms using the Quick Inventory of Depressive Symptomatology–Self-Report (36); perceived stress using the Perceived Stress Scale (37); interoceptive awareness using the subscales of noticing, emotional awareness, body listening, attention regulation, trusting, and not-distracting of the Multi-dimensional Assessment of Interoceptive Awareness (38); decentering using the Experiences Questionnaire—decentering factor (39); mindfulness skills using the Five Factor Mindfulness Questionnaire, short version (40); and trait rumination using the Rumination Response Scale (41).

### Neural Connectivity

The outcome measure of the primary mechanisms was change in neural connectivity measured using fMRI. We selected the DMN and the SN as a priori networks of interest.

Given the novelty of the design, it was difficult to estimate the statistical power. Hence, we based our estimation of power on a recent guideline by Poldrack *et al.* (42) suggesting that 28.5 to 30 participants per group give 80% power for medium to large effects and an earlier and frequently cited guideline

## Mindfulness Changes Brain Dynamics During Rumination

(43) that suggested only 20 to 30 participants per group to allow for small to medium fMRI effects. Giving more weight to the latter more stringent estimation, we allocated 50 participants in the MBCT group and 30 in the control group, allowing for more attrition in the MBCT group.

### MRI Paradigm

The fMRI paradigm included a structural scan and 4 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 (for further details of the MRI paradigm and rationale, see [Extended Methods and Materials](#) in the [Supplement](#)).

Each state was followed by experience sampling in the scanner, assessing affective, cognitive, and somatic experiences, adapted from the study by Smallwood *et al.* (44) ([Table S1](#)). The rating items were presented on a computer screen in the scanner using a visual analog scale, in which the degree of agreement from 0% to 100% could be indicated by moving a cursor on the scale with a trackball.

**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 the study by Karl *et al.* (45) 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.

**Mindfulness Meditation Instructions.** During the mindfulness meditation state, participants were guided through the breathing space of the MBCT program to become aware of the present moment thoughts, feelings, and bodily sensations and were encouraged to embody an attitude of curiosity and acceptance. Participants were scanned at baseline and within a month after treatment.

### MRI Acquisition and fMRI Preprocessing

Functional and structural images of the brain were acquired on a 3T Siemens Magnetom Skyra 3T scanner (software version Scout; Siemens Healthineers) using a 32-channel head coil. Four fMRI scans, each of 5-minute duration, were acquired to evaluate how states of rest, mindfulness, and rumination affected functional connectivity, with a second resting state between the mindfulness and rumination state. We used FSL tools [version 6.0] (46) for preprocessing. Preprocessing steps followed standard procedures and included registering the functional to the structural image, registering the structural image to standard space, motion correction, spatial smoothing, and a high-pass filter. Finally, data were high-pass filtered (100-second cutoff) (for full details, see the [Extended Methods and Materials](#) in the [Supplement](#)).

### Analyses

**Clinical Efficacy and Mechanism Analyses.** Effects on self-report clinical measures and questionnaires were analyzed

using multilevel models. See [Extended Methods and Materials](#) in the [Supplement](#) for full details of the analysis procedures.

**fMRI Analyses: fMRI Seed Region Extraction.** To derive seed regions for the SN and DMN, we used a previously published and widely used set of brain network maps (47). For each participant, time courses were extracted for each network mask as the first eigenvariate using `fslmeants`.

**fMRI Analyses: Group Comparisons.** We compared SN and DMN connectivity with the rest of the brain as a result of treatment, i.e., group  $\times$  time interactions. First, we obtained connectivity maps (contrast of parameter estimates) between the a priori networks and the rest of the brain using regression analysis using `fsl_glm`, separately for each participant and condition. We then computed change as pretreatment minus posttreatment contrast of parameter estimates.

We compared the randomized groups using nonparametric permutation testing with threshold-free cluster enhancement from FSL's `randomise` (48). Results were thresholded at  $p < .05$  (two-tailed). We corrected for multiple comparisons across the 2 a priori networks and the 3 unique scan conditions (rest, mindfulness, and rumination) using the Bonferroni method (49).

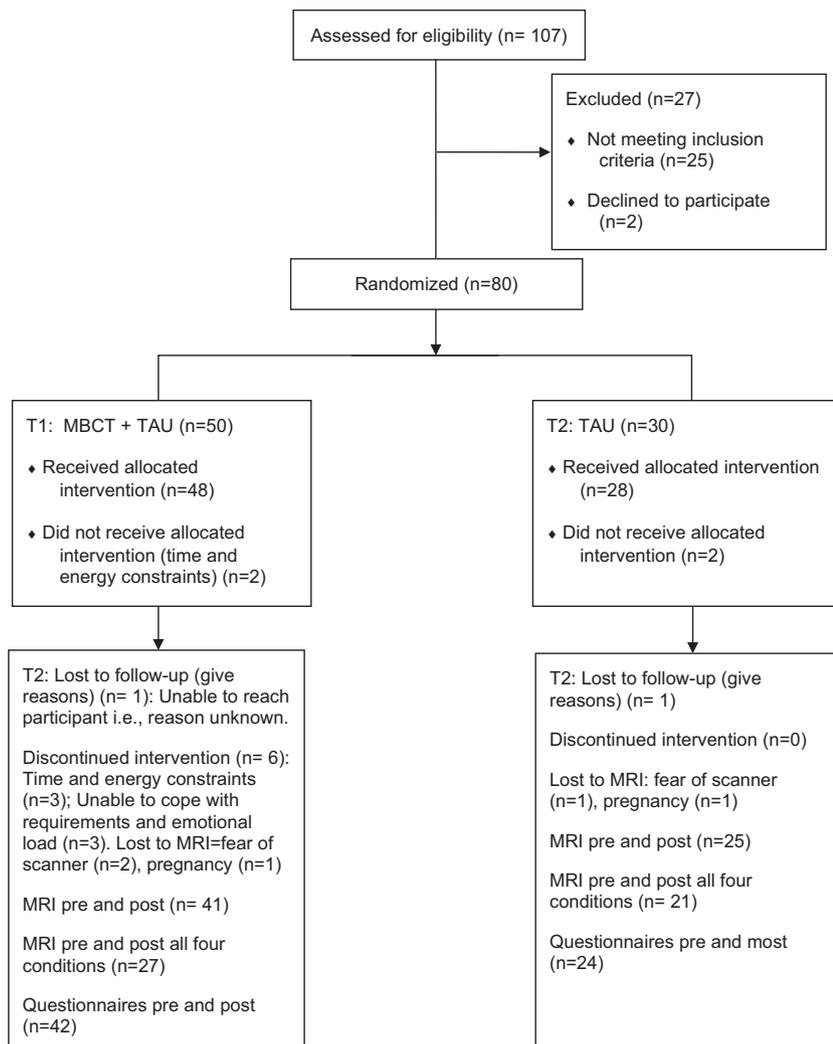
For completeness, we also performed exploratory analyses across all networks and selected seeds using nonparametric permutation testing using threshold-free cluster enhancement, but without applying familywise error correction across networks.

### Relating Neural Connectivity to Psychological Processes via Questionnaires and Experience Sampling Measures

We compared all the statistically significant group  $\times$  time changes (neural connectivity and psychological processes using partial correlation analyses, controlling for group assignment to access robust relationships that would not just be a marker of treatment effect. We applied Bonferroni corrections (49) for multiple comparisons across significant neural and significant questionnaire findings and followed up significant results using bootstrapped mediation analysis using MATLAB (version 9.1; The MathWorks, Inc.) (50).

## RESULTS

Between February 2017 and February 2018, 107 participants were assessed for eligibility using structured clinical interviews (DSM-IV-TR), and 80 patients were recruited. Subsequently, the participants were randomly allocated to receive MBCT in addition to TAU ( $n = 50$ ) or TAU alone ( $n = 30$ ) ([Figure 1](#)). Baseline characteristics were balanced between the groups on all demographic and psychiatric variables and questionnaire scores ([Table 1](#)). The number of participants with depressive symptoms in the symptomatic range (Quick Inventory of Depressive Symptomatology–Self-Report  $> 5$ ) was 58 of 78 (74%). The rumination condition of the fMRI paradigm was voluntary because of ethical reasons. Those not undertaking the rumination condition ( $n = 20$ ) had higher baseline depressive symptoms ([Table S2](#)). No serious adverse events occurred.



**Figure 1.** Participant flow. MBCT, mindfulness-based cognitive therapy; MRI, magnetic resonance imaging; TAU, treatment as usual.

### Clinical and Behavioral Assessments

MBCT treatment compared with TAU reduced depressive symptoms ( $p = .001$ ,  $g = 0.82$ , 95% CI,  $-6.47$  to  $-1.78$ ) and increased dispositional mindfulness skills ( $p < .001$ ,  $g = 0.68$ , 95% CI,  $1.49$  to  $9.57$ ), decentering ( $p < .001$ ,  $g = 0.98$ , 95% CI,  $3.76$  to  $11.01$ ), and interoceptive awareness (Figure 2) including the ability to notice bodily sensations ( $p < .001$ ,  $g = 0.95$ , 95% CI,  $1.60$  to  $4.76$ ), awareness of the manifestation of emotions in the body ( $p < .001$ ,  $g = 1.10$ , 95% CI,  $2.82$  to  $7.12$ ), active listening to the body for insight ( $p < .001$ ,  $g = 1.19$ , 95% CI,  $1.63$  to  $3.85$ ), and the ability to sustain and control attention to body sensations ( $p < .001$ ,  $g = 1.00$ , 95% CI,  $2.56$  to  $7.44$ ). We found no significant interaction effects on the ruminative response scale measuring trait rumination ( $p = .25$ ), either as full scale or as subscales, i.e., brooding ( $p = .21$ ,  $g = 0.29$ , 95% CI,  $-0.61$  to  $2.74$ ), reflection ( $p = .64$ ,  $g = 0.11$ , 95% CI,  $-1.62$  to  $1.00$ ), or depression ( $p = .14$ ,  $g = 0.35$ , 95% CI,  $-0.88$  to  $5.87$ ), or on the Multidimensional Assessment of Interoceptive Awareness not-distracting ( $p = .052$ ,  $g = 0.11$ , 95% CI,  $-0.62$

to  $0.31$ ) or trusting ( $p = .01$ ,  $g = 0.07$ , 95% CI,  $-0.65$  to  $0.43$ ) subscales.

### Neural Results

**Manipulation Check of fMRI Paradigm.** As a manipulation check, we asked participants about their experiences after each scan (Figure 2; Figure S1). As expected, rumination strongly increased negative self-related thoughts and decreased body awareness compared with all other conditions (Figure 3A). In contrast, mindfulness induction led to fewer negative self-related thoughts and increased body awareness compared with both resting state and the rumination state. However, MBCT compared with TAU did not significantly change experiencing sampling reports of body awareness in the rumination condition ( $p = .86$ ,  $g = -0.05$ , 95% CI,  $-0.62$  to  $0.52$ ,  $t_{47} = -0.18$ ). While there was a general reduction of negative self-related thoughts across states comparing MBCT with TAU ( $F_{1,47} = 15.77$ ,  $p < .001$ ,  $\eta^2 = 0.015$ ), this trend did not reach significance in the rumination condition ( $p = .39$ ,

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**Table 1. Baseline Characteristics**

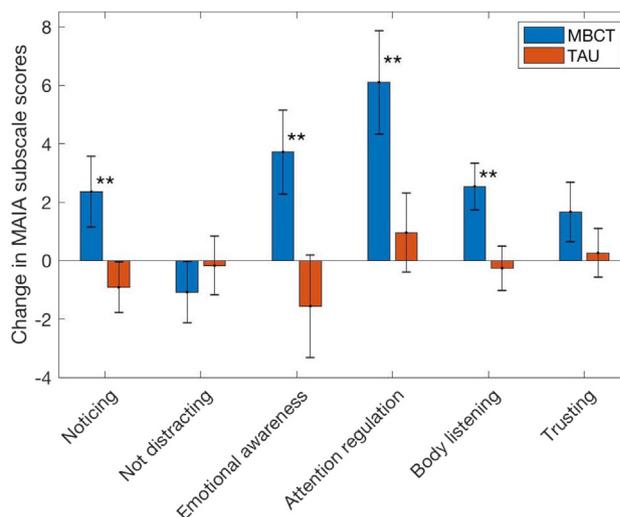
	MBCT+TAU, N = 50	TAU, N = 30
Sociodemographic Characteristics		
Age, Years	43.17 (14.22)	45.25 (12.01)
Sex, Female/Male	35/15 (70%)	23/5 (82%)
Educational Level		
Low (<2-year further education)	15 (30%)	3 (11%)
Medium (2–4-year further education)	24 (48%)	21 (75%)
High (>5-year further education)	9 (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		
Symptomatic (QIDS > 5)	43 (83%), n = 50	25 (76%), n = 28
Antidepressant Usage	43/7 (86%), n = 50	21/7 (75%), n = 28
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		
QIDS (36)	9.23 (4.58)	9.68 (5.10)
EQ (39)	31.43 (7.12)	31.26 (7.06)
MAIA_AR (38)	17.22 (5.03)	17.78 (4.99)
MAIA_BL (38)	6.25 (2.07)	7.40 (3.25)
MAIA_TR (38)	8.89 (3.31)	8.40 (3.77)
MAIA_NO (38)	12.79 (2.61)	13.96 (3.38)
MAIA_ND (38)	9.17 (2.64)	9.01 (2.45)
MAIA_EA (38)	15.32 (3.51)	16.57 (4.23)
FFMQ (40)	44.21 (8.88)	45.33 (80.2)
RRS (41)	53.38 (9.80)	57.51 (8.24)

Values are presented as *n*, *n* (%), and mean (SD).

AR, attention regulation; BL, body listening; EA, emotional awareness; EQ, Experience Questionnaire; FFMQ, Five Factor Mindfulness Questionnaire; MAIA, Multidimensional Assessment of Interoceptive Awareness; ND, not-distracting; NO, noticing; MBCT, mindfulness-based cognitive therapy; QIDS, Quick Inventory of Depressive Symptomatology; RRS, Rumination Response Scale; TAU, treatment as usual; TR, trusting.

$g = -0.25$ , 95% CI,  $-0.82$  to  $0.33$ ,  $t_{47} = -0.87$  (Figure 3B; other conditions in Figure S3).

**Change in Neural Connectivity as a Function of Treatment.** We tested whether MBCT changed neural connectivity between either the DMN or SN and the rest of the brain across the different scan conditions. For the DMN, we found no significant group  $\times$  time differences. For the SN, we found that connectivity was changed during the rumination condition ( $n = 48$ ) as a function of treatment.



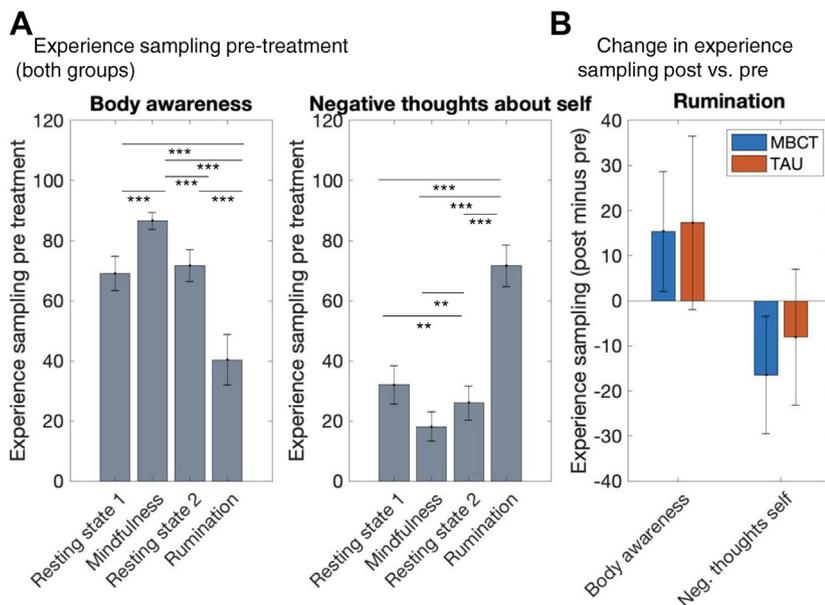
**Figure 2.** Change in the dimensions of interoceptive awareness as a function of treatment. Subscales of the Multidimensional Assessment of Interoceptive Awareness Questionnaires (MAIA) (39) differences between post and pretreatment on preselected subscales of 1) noticing: awareness of uncomfortable, comfortable, and neutral body sensations, 2) not-distracting: tendency not to ignore or distract oneself from sensations of pain or discomfort, 3) emotional awareness: awareness of the connection between body sensations and emotional states, 4) attention regulation: ability to sustain and control attention to body sensations, 5) body listening: active listening to the body for insight, and 6) trusting: experience of one's body as safe and trustworthy. Mindfulness-based cognitive therapy (MBCT) caused increases on all subscales, apart from the not-distracting subscale. Error bars show 95% confidence intervals. \*\* $p < .01$  for  $t$  tests comparing the groups. TAU, treatment as usual.

In particular, we found changes in SN connectivity with both the right lingual gyrus and the left lateral occipital cortex (lingual gyrus:  $x = 14$ ,  $y = -64$ ,  $z = 0$ ; extend: 85 voxels, maximum  $t$  value = 6.25, minimum  $p = .0072$  [two-tailed]; lateral occipital cortex:  $x = -52$ ,  $y = -82$ ,  $z = 16$ , extend: 16 voxels, maximum  $t$  value = 5.93, minimum  $p = .015$  [two-tailed]) (Figure 4).

Next, we tested whether the group differences (MBCT vs. TAU) were present preintervention or postintervention. We found that the groups did not differ pretreatment (occipital: Mann-Whitney  $U_{56} = 491$ ,  $p = .13$ , rank biserial correlation = 0.24; lingual gyrus: Mann-Whitney  $U_{56} = 453$ ,  $p = .37$ , rank biserial correlation = 0.14). Instead, the MBCT group showed reduced connectivity between SN and both regions of occipital cortex (Mann-Whitney  $U_{47} = 134$ ,  $p = .001$ , rank biserial correlation =  $-0.54$ ) and lingual gyrus (Mann-Whitney  $U_{47} = 152$ ,  $p = .004$ , rank biserial correlation =  $-0.48$ ) posttreatment; for completeness, see Figure S4 for other scan conditions.

Subsequently, we corrected for multiplicity across both a priori networks of interest (SN and DMN) and the unique scan conditions (rest, mindfulness, and rumination). We found that only SN connectivity to the lingual gyrus remained significant (i.e., two-tailed  $p$  value with Bonferroni correction  $< .0083$ ).

**Relating Neural Connectivity During Rumination to Self-reported Psychological Processes.** To understand how changes in neural connectivity and psychological processes were related, we correlated the changes in connectivity between the SN and lingual gyrus and occipital cortex to



**Figure 3.** Change in experience sampling after each state: 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)** Change in experience sampling ratings after treatment per group during the rumination scan. Error bars show 95% confidence intervals. \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ , significance stars in **(A)** is for within-subject  $t$  tests comparing the different scan conditions and in **(B)** is for  $t$  tests comparing the groups. MBCT, mindfulness-based cognitive therapy; Neg., negative; TAU, treatment as usual.

significant changes in questionnaire and experience sampling scores (correcting for multiple comparisons and group, see [Methods and Materials](#)). Connectivity change between the SN and lingual gyrus was associated with self-reported increased ability to sustain and control attention to body sensations, measured using the attention regulation subscale of the interoceptive awareness (Multidimensional Assessment of Interoceptive Awareness) questionnaire. Specifically, higher ratings on the attention regulation subscale related to more decoupling of the SN from the lingual gyrus ([Figure 5A](#)) ( $p = .0001$ ,  $r = -0.55$ , 95% CI,  $-0.73$  to  $-0.31$ ), using partial correlation with familywise error correction for a total of 22 tests with the  $p$  threshold for Bonferroni correction  $< .0027$ . This correlation was also found separately in the MBCT ( $p = .004$ ,  $r = -0.54$ , 95% CI,  $-0.77$  to  $-0.19$ ) and the TAU ( $p = .006$ ,  $r = -0.63$ , 95% CI,  $-0.84$  to  $-0.22$ ) groups. No other partial correlations reached significance when correcting for multiple comparisons (see [Table S5](#) for a full list of uncorrected correlations per group). Examining the relationship between treatment, neural change, and psychological processes further revealed that the neural change mediated the increased ability to sustain and control attention to body sensations (indirect effect  $a \times b = 3.65$ , bootstrapped CI, 1.09 to 6.59,  $p = .0007$ ), explaining 57% of the effect ([Figure 5B](#)).

Furthermore, explorative comparisons across all 17 Yeo networks and subcortical seeds of the amygdala, hippocampus, and striatum related to the whole brain, identified a change in the amygdala linked to similar visual areas and a change in the somatomotor network during rumination ([Figure S6](#)).

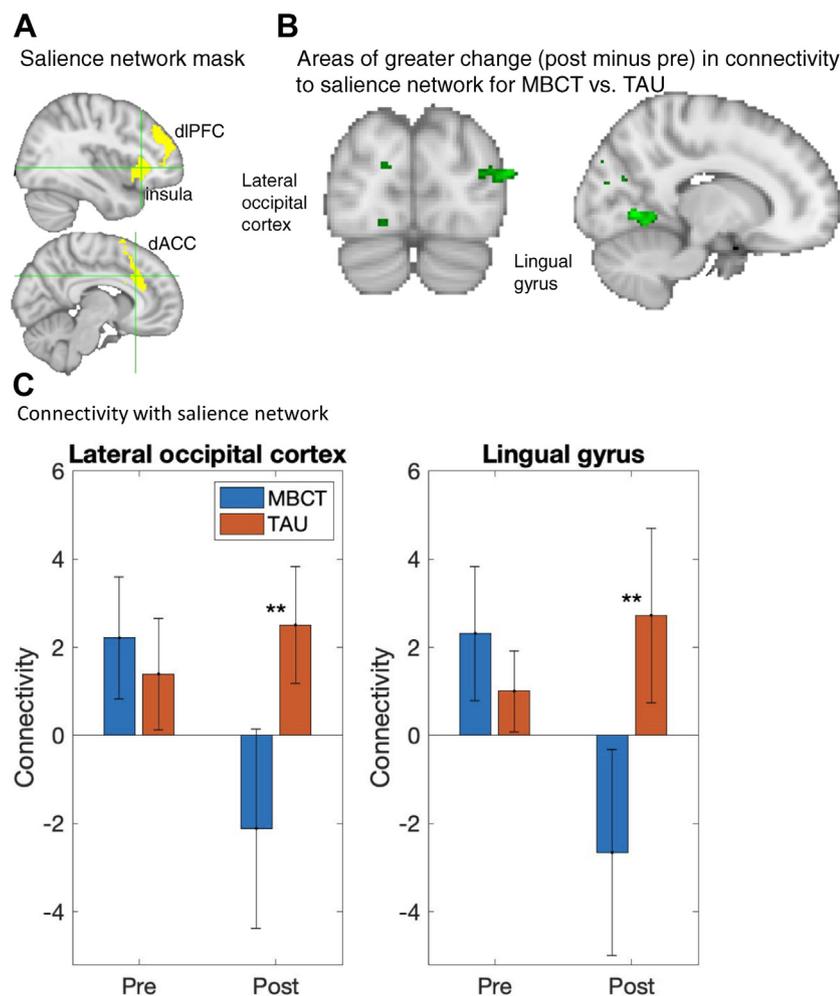
## DISCUSSION

MBCT is an effective treatment for recurrent depression. To understand the MBCT neurocognitive mechanisms of action,

we measured neural connectivity and concurrent psychological processes across experimentally induced states of rest, mindfulness practice, and rumination in a randomized controlled trial comparing the effect of MBCT versus TAU. 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 3 states (rest, mindfulness, and rumination). MBCT compared with TAU led to decreased functional connectivity between SN connectivity and both the lingual gyrus and occipital cortex during the ruminative state. However, only the connectivity to the lingual gyrus was significant after correcting for multiple state and network comparisons. No change was found in the mindfulness and resting states or in the DMN seed as a function of treatment. Change in SN connectivity to the lingual gyrus was mediated by the ability to sustain and control attention to body sensations.

Our findings are consistent with a growing body of literature indicating a central role for the SN in depression symptomatology and treatment response ([13,20,24–26,28](#)). Activation in areas of the SN, such as the anterior cingulate cortex and insular cortex, have been found to predict treatment response across various forms of psychotherapy for depression ([13](#)), predict change in response to mindfulness-based interventions across a wide group of populations ([11,12](#)), and modulate depressive symptoms after mindfulness training among healthy participants ([29](#)). SN connectivity may also play a key role in negative bias, valence, and persistence of depressive rumination ([32](#)). The lingual gyrus is a multimodal association cortex, which, during depression, has been associated with vision, episodic memory, and emotional processing ([51–56](#)), whereas the occipital cortex has been associated with visualization of painful experiences, memory retrieval, and emotional processing, e.g., ([57](#)). While the uncoupling of SN

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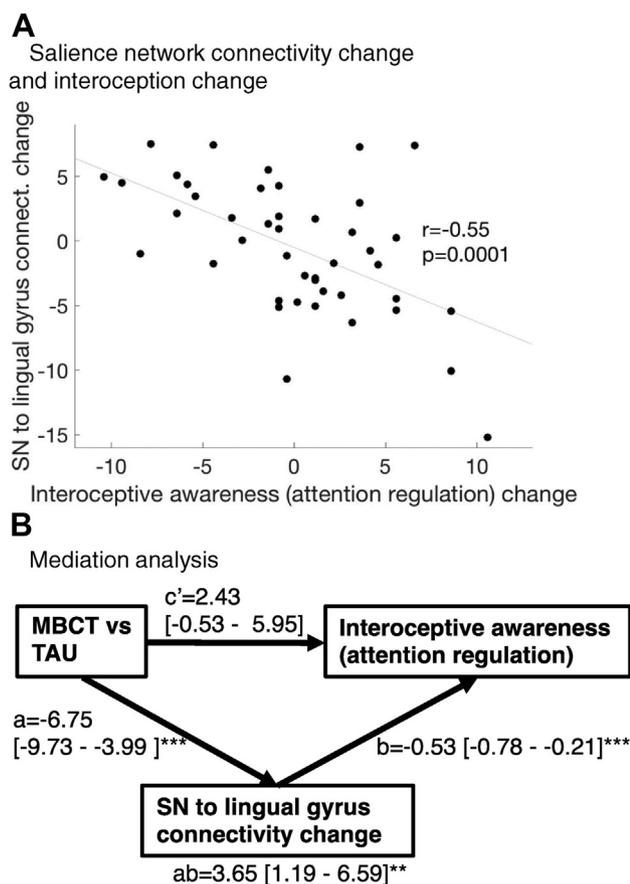
**Figure 4.** Change in neural connectivity during rumination as a function of treatment ( $n = 48$ ). **(A)** The mask for the salience network (SN) included the dorsal anterior cingulate cortex (dACC), dorsolateral prefrontal cortex (dlPFC), and anterior insula. **(B)** Comparing the effect of mindfulness-based cognitive therapy (MBCT) vs. treatment as usual (TAU) on change in connectivity (post minus pre MBCT/TAU) with SN. Connectivity is changed to the lateral occipital cortex and lingual ( $p < .05$ , two-tailed, cluster-corrected). **(C)** Connectivity between SN and lateral occipital cortex (left) and lingual gyrus (right) separately for pre- and posttreatment and for the MBCT (blue) and the control group (red). In both areas, MBCT decreased the connectivity to SN compared with TAU posttreatment, while there was no difference between the groups pretreatment. Error bars show 95% confidence intervals. \* $p < .05$ , \*\* $p < .01$  for two-tailed  $t$  tests comparing the 2 groups.

connectivity from the 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 because this neural uncoupling was associated with improvements in the ability to sustain and control attention to bodily sensations.

We did not find evidence of a reduction in dispositional rumination, negative self-related thought during the ruminative state, or change in the DMN connectivity. It is possible that this is because of lack of statistical power to detect small effects (i.e., both trait rumination and negative self-related thoughts showed a statistically nonsignificant trend toward reduced scores after MBCT with small effect sizes). Another possibility is that individuals with recurrent depression remain prone to engaging in negative self-related thinking after treatment, and hence, negative self-related thoughts do not change much. The findings on rumination as a putative mechanism have been inconsistent to date, and the field has been debating possible reasons for this (58–61). Dispositional measures of rumination tend to focus on ruminative thought content rather than

ruminative processes characterized by poor executive control, negative memory bias, and the persistence or stickiness of negative mind states (59,62). Yet, the MBCT program does not focus on changing ruminative thought frequency or content, but rather on the ability to recognize, decenter, and disengage from such thoughts, thus reducing the risk of spiraling downward into a depressive mood and the potential onset of relapse (6). Furthermore, it has been proposed that the DMN and SN may play different roles in depressive rumination, with the SN being more related to persistence, “stickiness,” and inability to disengage from the ruminative state persistence, and the DMN being more related to the self-referential thought content (32). Hence, it may not so much be the prevalence of negative self-related thought content that changes during a ruminative state, but rather the persistence and stickiness of the ruminative state, and perhaps the change in SN connectivity along with the ability to sustain and control attention to the body play a role in the persistence of a ruminative state.

Explorative analyses also identified a change in amygdala to lingual gyrus connectivity and the somatomotor network during rumination due to MBCT treatment compared with TAU.



**Figure 5.** Associations between change in neural connectivity and change in concurrent psychological processes. **(A)** Partial correlation (controlling for treatment group) between change in neural connectivity between the salience network (SN) and lingual gyrus and change in self-reported ability to sustain and control attention to body sensations, measured using the attention regulation subscale of Multidimensional Assessment of Interoceptive Awareness. **(B)** The effect of mindfulness-based cognitive therapy (MBCT) vs. treatment as usual (TAU) on the ability to sustain and control attention to body sensations (i.e., Multidimensional Assessment of Interoceptive Awareness attention regulation subscale) is mediated by decrease in connectivity between the SN and lingual gyrus, explaining 57% of the effect. When accounting for the indirect (mediation) effect of changed SN to lingual gyrus connectivity, the intervention effect is no longer significant, suggestion full mediation. \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ , \*\*\*\* $p < .0001$  for significance of the paths in the mediation model. connect., connectivity.

The amygdala is often viewed as an extension of the SN and plays a role in emotional processing during depression (32), and the amygdala and sensory areas of the somatomotor network have been related to mindfulness training (11); 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 priori and further determine how change in these regions relates to psychological constructs and clinical outcomes.

The study had a number of limitations. We chose TAU as the control group because we wanted to know how the

intervention of MBCT as a whole affected neural change. 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 with equally effective treatment practices of MBCT drive the neural change by using a dismantling design or active attention control. While the MBCT teachers were highly experienced, fulfilling internationally recognized good practices guidelines for teachers, trainers, and supervisors of mindfulness courses (35), we did not directly measure their adherence to the treatment protocol and teaching competency (e.g., Mindfulness-Based Interventions: Teaching Assessment Criteria) during the programs. Because of ethical reasons, participants could opt out of the rumination condition, meaning that the neural findings can only be generalizable to participants who were 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.

In conclusion, MBCT compared with TAU led to decreased functional connectivity between SN connectivity and the lingual gyrus during a ruminative state, and this neural change mediated an increased ability to sustain and control attention to body sensations. These findings demonstrate that the clinically effective MBCT intervention can modulate neuro-cognitive functioning during depressive rumination and the ability to sustain attention to the body.

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AMvdV, AR, and WK were responsible for the original proposal, and AMvdV secured funding for the trial. AMvdV developed the design and protocol, and AR, WK, JSm, CJH, and SWL advised on the design. AMvdV was responsible for the general management of the study, and LOF oversaw the clinical management of the study. AMvdV, E-ME, and LOF collected the data. JSm, JSc, AMvdV, AR, and WK created the analysis strategy. JSc analyzed the MRI data, and JSc and MSO analyzed the self-report data and clinical data. JSc, AMvdV, JSm, SWL, CJH, MSO, AR, and WK interpreted the data. JSc and AMvdV wrote the initial draft of the methods and results, and AMvdV wrote the initial draft of the introduction and discussion. All authors contributed to and approved the final manuscript.

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## ARTICLE INFORMATION

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