Original Article

Effects of a Mindfulness-Based Intervention on Cancer-Related Cognitive Impairment: Results of a Randomized Controlled Functional Magnetic Resonance Imaging Pilot Study

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BACKGROUND: Many breast cancer survivors suffer from cognitive complaints after cancer treatment, affecting their quality of life. The objective of this pilot study was to investigate the effect of a blended-care mindfulness-based intervention (MBI) on chemotherapy-related cognitive impairment and functional brain changes. Furthermore, correlations between changes in cognitive functioning and self-reported behavioral factors were investigated. **METHODS:** Breast cancer survivors (n = 33) who reported cognitive impairment were randomly allocated to a mindfulness condition (n = 18) or a waitlist control condition (n = 15). Patients completed questionnaires on cognitive impairment, emotional distress, and fatigue; neuropsychological tests; and resting-state functional magnetic resonance imaging before the start of MBI (time 1 [T1]), immediately after the completion of an 8-week MBI program (T2), and 3 months postintervention (T3). Resting-state functional connectivity was estimated in the default mode network, the dorsal and salience attention networks, and the frontoparietal network. Mixed model repeated-measures analysis was performed to test the intervention effect. **RESULTS:** Patients in the mindfulness condition exhibited significantly higher connectivity between the dorsal and salience attention networks after the mindfulness intervention compared with those in the control condition. MBI participants also had reduced subjective cognitive impairment, emotional distress, and fatigue. No intervention effect was observed on neurocognitive tests. **CONCLUSIONS:** MBI may induce functional brain changes in networks related to attention and may have a positive effect on subjective measures of cognitive impairment in breast cancer survivors. Therefore, MBI could be a suitable intervention to improve quality of life in this population and deserves further study in this context. ***Cancer* 2020;0:1-10**. *© 2020 American Cancer Society*.

KEYWORDS: attention network, breast cancer, cognitive impairment, default-mode network, functional magnetic resonance imaging (fMRI), mindfulness-based intervention, resting state.

INTRODUCTION

The prevalence of cognitive complaints in patients with cancer has become an important area of research. There is increasing evidence that treatments for noncentral nervous system tumors can have both acute and long-term effects on cognitive functioning.[1,2] Women who are treated for breast cancer for example, regularly report problems with cognitive processes involving memory, attention, and executive functioning. These cognitive deficits can be a worrying side effect of cancer and its treatment and can have a serious effect on quality of life. The incidence of posttreatment cognitive problems detected by neurocognitive tests in patients with cancer ranges from 19% to 78%.[3] However, the course and duration of treatment-related cognitive dysfunction are largely unknown. Incidence is higher immediately

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after the completion of treatment.[1,3] Whereas a group of women shows (partial) recovery at 1 year postchemotherapy,[4] others still experience cognitive dysfunction 10 to 20 years after treatment.[5,6]

There is currently a high need for therapeutic interventions that can reduce these cognitive complaints after cancer treatment. Preliminary evidence indicates that an intervention based on mindfulness can have a positive effect on cognitive functioning in patients with cancer.[7] Mindfulness refers to a compassionate and nonjudgmental, moment-to-moment awareness of one's experiences.[8] Two common interventions to teach mindfulness skills are *mindfulness-based stress reduction* (MBSR)[9] and *mindfulness-based cognitive therapy* (MBCT).[10] Both programs follow a structured curriculum, which is taught in a group over 8 weeks. Participants develop skills in their capacity to become nonjudgmentally aware of thoughts, feelings, and sensations. They increase their capacity to replace automatic, habitual, and often judgmental reactions with more conscious and skillful responses. Over the past 20 years, mindfulness-based interventions (MBIs) have become increasingly popular in psychosocial care for patients with cancer and cancer survivors[11,12] and have shown efficacy in reducing a range of cancer-related symptoms, such as levels of anxiety and depression,[13-15] sleep disturbance,[16] fatigue,[17-19] and fear of cancer recurrence.[20,21] However, studies investigating the effects on cancer-related cognitive impairment are largely missing. To our knowledge, until now, only 1 study has examined the effects of MBSR on cancer-related cognitive impairment using both subjective and objective assessments.[7] The effects of MBSR, compared with an active control group (fatigue education and support), were tested in breast and colorectal cancer survivors who had moderate-to-severe fatigue using a randomized clinical trial. The authors noted significantly greater improvement, compared with controls, on perceived cognitive impairment immediately after the MBSR training and 6 months later, with moderate-to-large effect sizes. A similar pattern was observed for the objective outcomes on the Stroop test. MBSR participants made significantly fewer errors relative to the control group, and their accuracy rate increased over time. The effects were small to moderate. These results support the potential of MBSR as an intervention to relieve cancer-related cognitive impairment for fatigued cancer survivors. However, because the authors used only 2 cognitive measures, insight into the broader effect of MBSR on cognitive functioning and its relation to emotional well-being and associated brain mechanisms is still limited.

The objective of the current randomized controlled pilot study was to examine the effect of an MBI on different outcomes related to chemotherapy-induced cognitive impairment. Therefore, we not only assessed subjective and objective outcomes on cognitive functioning, but we also evaluated the potential recovery of brain changes in attention and default mode networks (DMNs) that have been observed after chemotherapy, using resting-state functional magnetic resonance imaging (rs-fMRI).[22-24] Functional MRI (fMRI) allows the indirect observation of brain activation using the vascular response of nearby electrically active neurons, ie, the blood oxygen level–dependent signal. When measured during rest (rs-fMRI), brain regions will show spontaneous blood oxygen level–dependent signal fluctuations. These fluctuations will happen in a synchronized way in brain regions that are functionally linked and thus allow us to investigate functional connectivity and brain networks at rest. Several studies have reported widespread changes to brain structure and function after chemotherapy.[25-27] By using fMRI, changes in brain activation have been observed during the execution of active tasks[25] as well as during rest (eg, in the attention and default mode network, a network that is involved in processes such as self-reflection, day dreaming, and rumination).[28-32] Interestingly, several recent reviews have demonstrated that practicing mindfulness meditation is associated with increased neural activation in brain regions related to external attention (ie, prefrontal and anterior cingulate cortex)[33-36] and reduced connectivity in the DMN involved in internal attention.[37,38]

We hypothesized that an MBI would have an effect on resting state functional connectivity in networks related to both external attention and internal attention and would reduce both objectively and subjectively assessed cognitive impairment. Our exploratory aim was to test for significant associations between changes in cognitive impairment, behavioral factors (ie, emotional distress, fatigue, mindfulness skills), and brain connectivity.

MATERIALS AND METHODS

Participants

Breast cancer survivors who experienced cognitive impairment were recruited over a 6-week period. Potential participants were identified at the Multidisciplinary Breast Cancer Center, University Hospitals Leuven. Participants were eligible if they were between ages 18 and 55 years, had a diagnosis of early stage breast cancer, had ended chemotherapy 6 to 24 months before enrolment, were premenopausal at the start of therapy, and had significant cognitive complaints, as measured by the Cognitive Failure Questionnaire (CFQ) (a CFQ total score > 42.9 [mean score from the study by Ponds et al[39]] ± 1 SD or a score ≥2 on the CFQ extra questions > the mean score from the study by Ponds et al ± 1 SD). Participants were excluded if they had previously participated in mindfulness training or if they had a history of intellectual disability, neurologic, or psychiatric disorders, such as depression or anxiety disorder. The study was approved by the local ethical commission and was conducted in accordance with the Declaration of Helsinki.

In total, 109 patients were contacted by mail and/or telephone. Thirty-nine showed interest in participating, of whom 5 were excluded because their scores on the CFQ were too low. The 34 eligible patients provided written informed consent and enrolled in the study.

Design and Study Procedures

The experimental design was a 2-arm randomized controlled trial using a waitlist-control condition. Randomization was done using an online random number generator by an independent researcher who did not participate in the assessments. Once participants were randomized, they were contacted by telephone for a brief orientation. Participants in the control condition could follow the MBI, including groupsessions and online support, after 5 months. Assessments were done at baseline (before randomization) (time point 1 [T1]), after the 8-week intervention period (T2), and 3 months postintervention (T3). The researcher collecting the data was blinded to the participants' group allocation.

Intervention

The MBI adhered to a standardized protocol developed from the MBSR curriculum[9] and MBCT developed for patients with cancer.[40] It was offered in a blended format, a combination of four 3-hour, in-person group sessions spread over 8 weeks and in between online support. Each session consisted of guided experiential mindfulness exercises (eg, focus on the breath, body scan, breathing space, mindful yoga, insight meditation, walking meditation), sharing of experiences of these exercises, reflection in small groups, psychoeducation (eg, stress, depression, fear of cancer recurrence, self-care), and review of home practices. The program objectives were: 1) to increase present moment awareness and recognize entanglement between one's thoughts, emotions, and bodily sensations; and 2) to teach acceptance and mindfulness as an alternative strategy for dealing with problematic thoughts and feelings and how these may be used to facilitate values-based actions. The program was led by a skilled facilitator following standardized procedures. The training was supported by the use of homework assignments and audio material. In between group sessions, participants were contacted by telephone or mail for a short check-up and a kind reminder to continue their daily practice.

Measures

Subjective and objective cognitive assessment

The CFQ was used to obtain information on subjective cognitive function[41] (for details, see Supporting Materials, Supporting Table 1, and Supporting Fig. 1).

Objective cognitive performance was evaluated using a neurocognitive test battery covering the following domains: 1) attention and concentration,[42,43] 2) memory,[43,44] 3) executive functioning,[43-47] and 4) cognitive/psychomotor processing speed.[43,44,48] In addition, the premorbid intelligence level[49] was estimated (for details, see Supporting Materials). Neuropsychological evaluation and MRI scans were performed on the same day.

fMRI imaging

All participants underwent imaging on a 3-Tesla scanner. During the acquisition of rs-fMRI, participants were asked to close their eyes, lay still, and not fall asleep (for details, see Supporting Materials).

Other measurements

Emotional distress was measured using the Depression Anxiety Stress Scales.[50] Fatigue was measured with the fatigue severity subscale of the Checklist Individual Strength.[51] The 37-item Comprehensive Inventory of Mindfulness Experiences was used to measure mindfulness[52] (for details, see Supporting Materials).

Statistical Analysis

Groups were compared at baseline using *t* tests. To test the intervention effect, we used a piecewise, multilevel model with 2 levels: time points (level 1) were nested within persons (level 2). In this model, 1) the dummy-coded assessment time (level 1 variable), 2) the treatment condition (level 2 variable), and 3) their cross-level interactions were included in predicting the outcome. Time points were coded by 2 dummy variables, T2 and T3, with T2 indicating the posttreatment periods (slope coded as 0 1 0) and T3 indicating the follow-up assessment (slope coded as 0 0 1). Condition

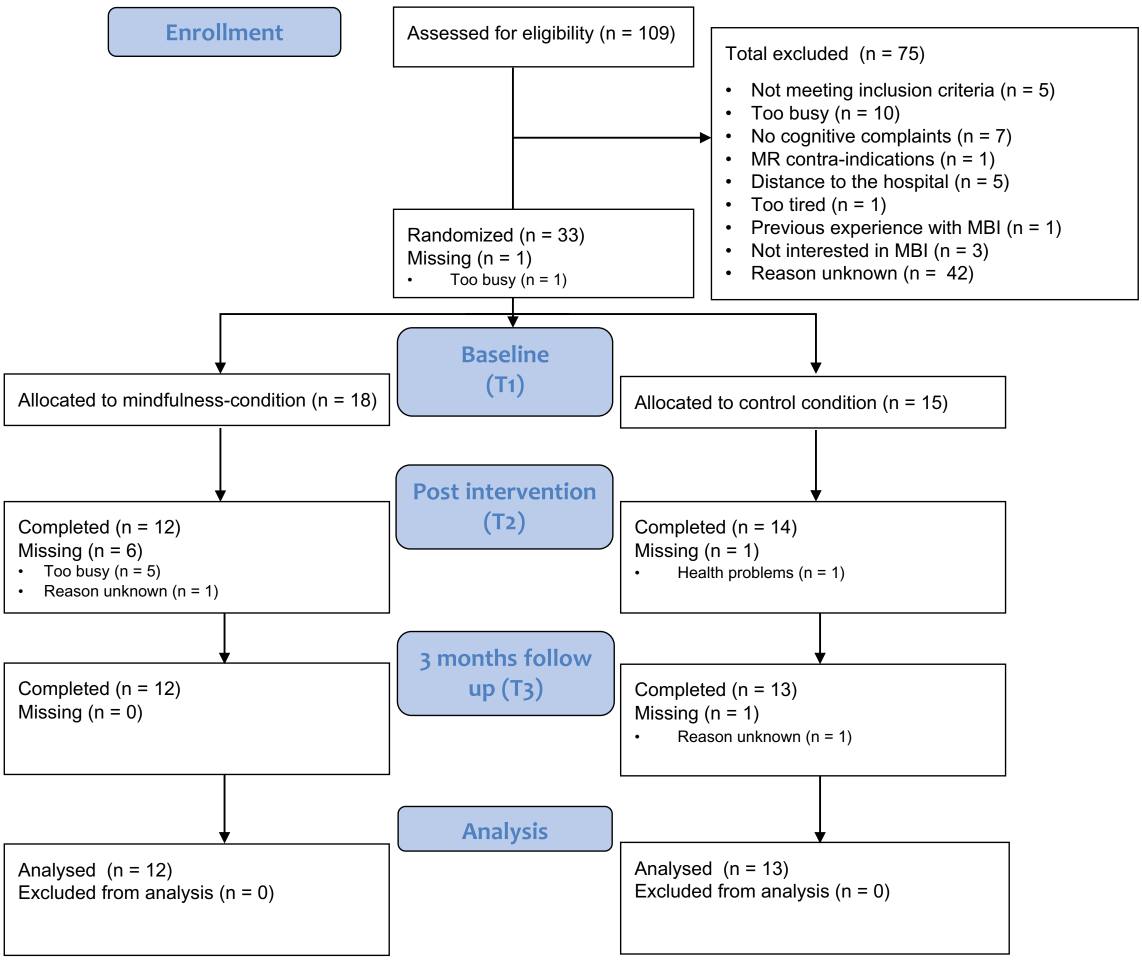

FIGURE 1. This is a CONSORT (Consolidated Standards of Reporting Trials) diagram illustrating the flow of participants through the trial. MR indicates magnetic resonance (scan); t1, time point 1 (before randomization); t2, time point 2 (immediately after the completion of an 8-week MBI program); t3, time point 3 (3 months postintervention).

was a dummy variable to represent the intervention condition (1) and the control condition (0). In the final model, intercepts and slopes were allowed to vary randomly across individuals. A corrected significance level was calculated for multiple comparisons according to the method described by Benjamini and Hochberg.[53]

Within-group effect sizes were calculated using Hedges g_{av}, which incorporates the correlation between measurements and provides a more accurate estimate in small samples.[54] Change scores were used to test associations between changes in cognitive impairment and behavioral outcomes.

Resting State-fMRI Data Analysis

Preprocessing of the rs-fMRI data and subsequent statistical analyses were performed with the CONN functional connectivity toolbox (NeuroImaging Tools & Resources Collaboratory) for all participants who completed the entire study, except for 1 who was excluded because of an image artifact (n = 24) (for details of the preprocessing steps, see Supporting Materials).

Region of interest (ROI)-to-ROI functional connectivity maps were generated for each participant, including the DMN, the salience and dorsal attention, and the frontoparietal network, as defined in the CONN toolbox (for details, see Supporting Materials). These networks were chosen because they have been associated before with aspects of cognitive changes after cancer treatment. Connectivity maps were subsequently used for second-level ROI-to-ROI–based analyses to study differences between groups and time points. A 2-sample t test was used to assess differences between groups at baseline in functional connectivity between ROIs. A 2 × 3 within-subjects, repeated-measures analysis of variance was used to assess group × time interaction effects in functional connectivity between ROIs. The significance threshold was set at $P < .05$ false discovery rate (FDR) corrected for multiple comparisons. ROI-to-ROI connections that showed significant interaction effects were selected to explore the relation with changes in neuropsychological outcomes using Pearson correlations.

RESULTS

Enrollment and Attrition

A CONSORT flow diagram on enrolment of participants in the study is given in Figure 1. In total 109 potential participants received a letter with a general outline of the study. Afterward, these candidates were contacted by phone to evaluate their interest. Patients interested to participate received the informed consent and the CFQ via mail. The researcher followed up by telephone to answer any questions related to the study. Only patients with a CFQ total score > 42.9 (mean score of study by Ponds et al) ± 1 SD or on ≥2 of the CFQ extra questions (> mean score from study by Ponds et al ± 1 SD[39]) were included in the study.

Baseline Characteristics

Demographic and medical information of the included patients is summarized in Table 1. All participants were women between ages 36 and 55 years. Their education levels were as follows: 45% finished secondary school, 45% held a higher education degree, the remaining 10% indicated that they never finished secondary school. Sixty-eight percent of the women were employed. The average time since completion of cancer treatment was approximately 1.58 years. Participants in the 2 conditions did not significantly differ on demographics or on any of the study variables at baseline.

Intervention Effects on Outcomes Based on Questionnaires

For the detailed, descriptive statistics on the outcomes at the 3 study data-collection time points, see Supporting Table 2. The condition × time interaction was significant at T2 and T3 for subjective cognitive impairment (see Table 2).[53] The effect at both time points was negative, suggesting that participants in the MBI condition, unlike those in the control condition, experienced a clear symptom reduction 1 week after the training (T2) and during follow-up (T3). A significant main effect of time was observed in the MBI condition (T2: $\beta = -12.77$; $P < .001$; T3: $\beta = -12.68$; $P < .001$). There was no significant main effect of time in the control condition (T2: $\beta = 0.15$; $P = .92$; T3: $\beta = -2.50$; $P = .12$). These effects remained significant after Benjamini and Hochberg correction for multiple testing. Within-group effect sizes were large and significant (.99 at T2 and .95 at T3) in the MBI condition. No significant effect sizes were observed in the control condition.

TABLE 1. Demographic and Clinical Characteristics of Included Patients

	No. of Patients (%)		
Characteristic	MBI Condition, n = 18	Control Condition, n = 15	*P*
Age: Mean ± SD, y	43.89 ± 6.03	47.4 ± 5.45	.27
Verbal IQ score: mean ± SD	112.61 ± 5.51	110.13 ± 10.35	.39
Medical treatment			
Radiotherapy	5 (42)	7 (58)	
Hormone therapy: Tamoxifen citrate	14 (54)	12 (46)	
Protocol of adjuvant chemotherapy			
EC → paclitaxel	12 (66)	11 (72)	
FEC → docetaxel	4 (22)	1 (7)	
Carboplatin + paclitaxel → EC	1 (6)	2 (14)	
Docetaxel + cyclophosphamide	1 (6)	1 (7)	

Abbreviations: →, Followed by, EC, epirubicin and cyclophosphamide; FEC, fluorouracil, epirubicin, and cyclophosphamide; MBI, mindfulness-based intervention.

We also observed a significant condition × time effect for emotional distress at both time points and for fatigue at follow-up (T3). The effect was negative, suggesting that participants in the MBI condition, unlike those from the control condition, experienced a clear symptom reduction. Only the interaction effect for emotional distress at follow-up remained significant after Benjamini and Hochberg correction. Within-group effect sizes for emotional distress and fatigue were medium to large and significant (emotional distress: .55 at T2 and .81 at T3; fatigue: .46 at T2 and 1.16 at T3). No significant condition × time effects were observed for total scores on the mindfulness skills.

Intervention Effects on Outcomes Based on Neurocognitive Testing

For the detailed, descriptive statistics of the outcomes at the 3 study data-collection points, see Supporting Table 3. We observed no significant condition × time effect for the outcomes based on neurocognitive testing (see Supporting Table 4).

TABLE 2. Results of Multilevel Model Estimating the Intervention Effect Piecewise at Time Points 2 and 3 on Outcomes Based on Retrospective Questionnaires

		T2 : Condition		T3 : Condition	
Questionnaire	Intercept ± SE	β ± SE	P[a]	β ± SE	P[a]
CFQ	48.03 ± 3.94	−12.74 ± 3.54[b]	<.001	−10.04 ± 3.59[c]	.007
Emotional distress	13.03 ± 1.92	−5.86 ± 2.51[d]	.025	−8.49 ± 2.27[b]	<.001
Fatigue	39.27 ± 2.54	−3.65 ± 2.28	.126	−9.41 ± 3.78[d]	.019
Mindfulness skills	132.61 ± 5.42	10.57 ± 6.49	.109	3.18 ± 6.57	.631

Abbreviations: CFQ, Cognitive Failure Questionnaire;SE, standard error; T2, time point 2; T3, time point 3.
[a]A corrected significance level of $P < .0312$ was used (Benjamini & Hochberg 1995[53]).
[b]$P < .001$.
[c]$P < .01$.
[d]$P < .05$.

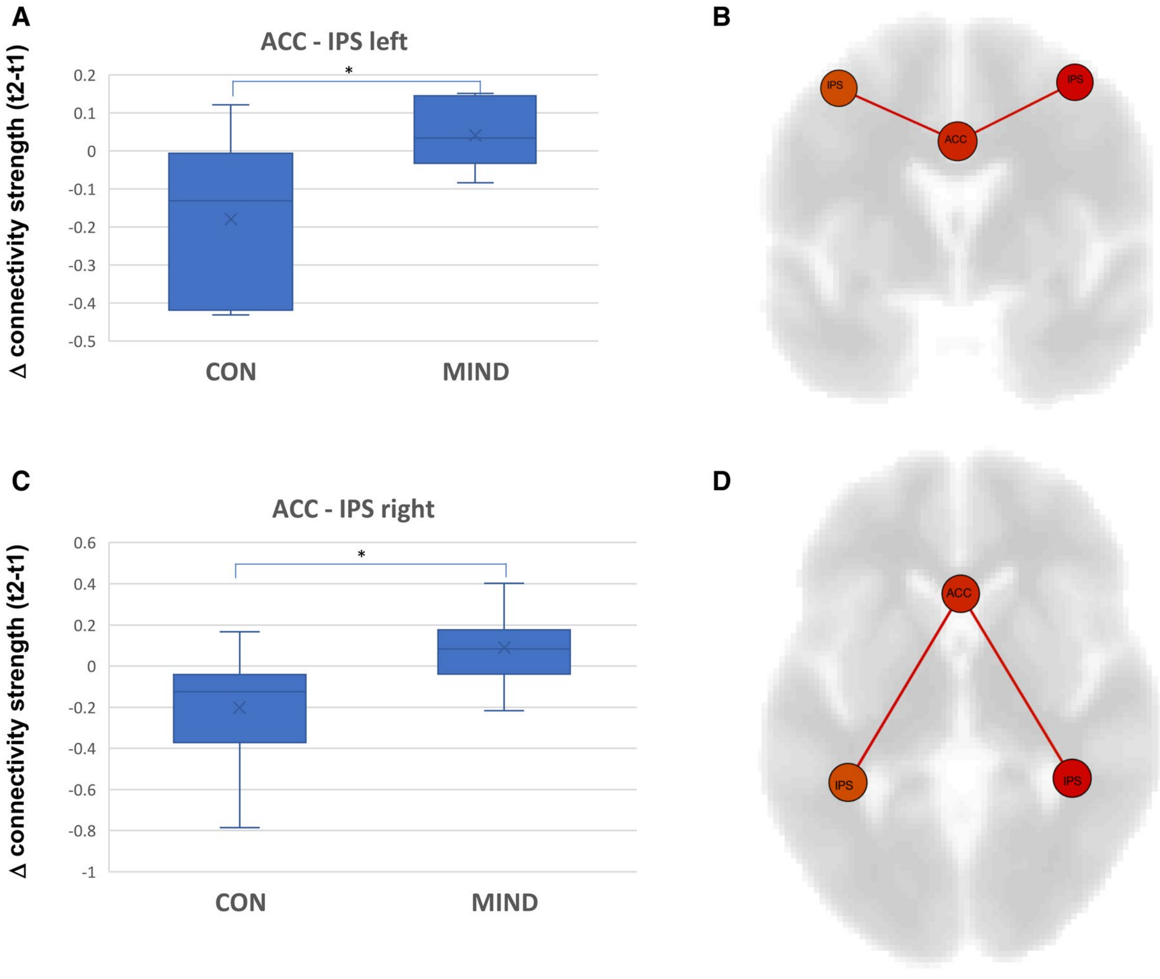

FIGURE 2. (A,C) Changes are illustrated in resting state functional connectivity strength between regions exhibiting a significant group × time interaction effect (asterisks: false-discovery rate [corrected], $P < .05$) at time point 2 (t2) > time point 1 (t1). (B,D) Visual representations on (B) coronal and [D] axial views of the regions showing a significant group × time interaction effect in resting state functional connectivity strength (false-discovery rate [corrected], $P < .05$) at t2 > t1. ACC indicates anterior cingulate cortex; CON, control condition; IPS, intraparietal sulcus; MIND, mindfulness condition.

Intervention Effects on Resting-State Functional Connectivity

The results indicated a significant condition × time effect with higher connectivity between regions of the attention networks in the MBI condition compared with the control condition. This higher connectivity was observed between the anterior cingulate cortex (ACC) (salience network) and both the left and right intraparietal sulcus (IPS) (dorsal attention network) (see Fig. 2). This effect, which was observed after FDR correction, was only significant at T2. No significant interaction effect was observed within portions of the DMN after FDR correction.

Relation Between Change in Functional Connectivity and Change in Behavioral Outcomes

To test potential associations, we calculated change scores for the significant outcomes based on the scores at baseline and at T2. Correlations (r) are shown in Supporting Table 5. After correction for multiple comparisons, a significant correlation was observed between the change in functional connectivity in the ACC and left IPS and the change in emotional distress ($r = -0.57$; $P = .004$). The correlation was negative, which suggests that stronger connectivity was associated with a reduction in symptoms of emotional distress.

DISCUSSION

Several studies have reported general benefits and efficacy of MBI in patients with cancer; however, studies investigating the effect of MBI on chemotherapy-related cognitive impairment and functional brain changes are scarce. We used rs-fMRI and subjective and objective measures of cognitive impairment to investigate the effect of a blended-care MBI in patients with breast cancer who were experiencing cognitive complaints and were assigned to an MBI condition versus a control condition.

In line with our hypothesis, the results revealed a significant condition × time interaction effect for functional connectivity within subregions of the attention networks, more specifically, higher connectivity between the ACC and both the left and right IPS, in the MBI condition compared with the control condition. Several neuroimaging studies examining changes in brain activation associated with breast cancer and chemotherapy have reported alterations in the networks responsible for attention and executive control.[25,27,28,55] Interestingly, a study investigating multitasking in patients with breast cancer showed reduced activity in both the ACC and the IPS after chemotherapy.[25] Our observation is in line with previous brain imaging studies showing an effect of mindfulness practice on attention-related networks.[35,56-58] Although several studies report increased activity in such networks after MBI, there is still large variation in studied subregions and the demonstrated effects across populations and tasks.[36] To our knowledge, this is the first observation of an effect of MBI within the attention networks in patients with cognitive impairment.

In contrast to our hypothesis and previous brain imaging studies on the effect of mindfulness,[37,38,59] we did not find a significant time × condition interaction effect within portions of the DMN. This might be because of the small sample size, as we did see a trend toward reduced connectivity in the DMN in the MBI condition compared with the control condition. However, this observation did not reach significance after FDR correction (see Supporting Fig. 2).

Also in line with our hypothesis, the results showed a significant condition × time interaction effect for subjective cognitive impairment. Participants in the MBI condition, unlike those in the control condition, experienced an improvement in subjective measures of cognitive impairment immediately after the MBI and at 3-month follow-up. This observation confirms the results reported by Johns et al.[7] In contrast to the findings by Johns et al, our current results demonstrated no effect on objective measures of cognitive functioning. A possible explanation for our null findings might be that there was no or very little room for improvement. The women in our study scored within normal ranges at baseline, with scores comparable to those reported in healthy controls.[26,60] It is also known that neuropsychological tests lack specificity and sensitivity to signal cancer-related cognitive impairment.[61] Future studies should use a more sensitive test battery for mild cognitive impairment.

The results also demonstrated that participants in the MBI condition, compared with those in the control condition, experienced a significant reduction in emotional distress and fatigue immediately after the training and at 3-month follow-up. This is in line with the most recent reviews[15,62]

An unexpected result was that we did not observe significant changes in mindfulness skills. It is well known in mindfulness research that the measurement of mindfulness skills is challenging. Recent findings suggest a lack of equivalence on a common, underlying, latent variable as well as a change in how the items are interpreted.[63] To date, there is only partial support for the differential sensitivity of mindfulness questionnaires to a change in mindfulness skills attributable to explicit mindfulness training.[64] It is also possible that the observed changes are partly because of nonspecific factors of group trainings, such as receiving attention of the trainer or group interactions, instead of the specific mindfulness meditation exercises. Therefore, future studies should attempt to replicate these results using an active control condition.

Despite the similarity in longitudinal changes in the brain connectivity pattern and behavioral changes, we only found a significant correlation with emotional distress. This result is in line with a recent study by Kardan et al,[65] who demonstrated that the change in functional connectivity after chemotherapy is a treatment symptom separate from the experienced cognitive impairment, fatigue, and emotional distress.

Strengths and Limitations of the Study

The strengths of our study include that, to our knowledge, this is the first trial to examine the effect of a blended-care MBI on cognitive impairment using biologic (rs-fMRI), behavioral, and psychological measures. By using rs-fMRI in this specific population, our current study demonstrates the potential *healing* effect of mindfulness when practiced by patients who are experiencing cognitive impairment. Our results support a future replication of this study using a larger sample size and an active control condition. Furthermore, the use of a blended-care program with only 4 face-to-face group sessions makes it feasible for participants who have a very busy life and could lead to future integration of the program into routine oncologic care. Because the intervention was led by a skilled facilitator, there is a potential effect of therapeutic alliance.

Limitations of the study include the small sample size, the lack of an active control condition, and a possible selection bias because of the low participation rate and the high attrition rate, which could have influenced the results. Generalizability is limited because the study population was composed of only patients with breast cancer. To further refine our understanding of changes in brain connectomics after MBI, ROI-independent, data-driven, multivariate network or graph analysis approaches could be used in future studies.

In conclusion, our findings demonstrate that a blended-care MBI may have a positive effect on subjective measures of cognitive impairment in breast cancer survivors and induce functional changes in attention-related networks. These findings suggest that MBI may help to decrease the burden of cancer-related cognitive impairment and thus can indirectly enhance quality of life in this population.

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CONFLICT OF INTEREST DISCLOSURES

Katleen Van der Gucht, Filip Raes, and Peter Kuppens are founders and members of the managing committee of the Leuven Mindfulness Centre Fund. Filip Raes and Katleen Van der Gucht receive payments for workshops and presentations related to mindfulness. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Katleen Van der Gucht: Conceptualization, formal analysis, funding acquisition, investigation, methodology, supervision, writing–original draft, and writing–review and editing. **Soumaya Ahmadoun:** Data curation, formal analysis, investigation, writing–original draft, and writing–review and editing. **Michelle Melis:** Investigation, writing–original draft, and writing–review and editing. **Ellen de Cloe:** Data curation, formal analysis, investigation, writing–original draft, and writing, review and editing. **Charlotte Sleurs:** Data acquisition, formal analysis, and writing–review and editing. **Ahmed Radwan:** Data curation, formal analysis, and writing–review and editing. **Jeroen Blommaert:** Data acquisition, formal analysis, and writing–review and editing. **Keisuke Takano:** Formal analysis, and writing–review and editing. **Mathieu Vandenbulcke:** Conceptualization, methodology, and writing–review and editing. **Hans Wildiers:** Conceptualization, methodology, and writing–review and editing. **Patrick Neven:** Conceptualization, methodology, and writing–review and editing. **Peter Kuppens:** conceptualization, methodology, and writing–review and editing. **Filip Raes:** Conceptualization, methodology, and writing–review and editing. **Ann Smeets:** conceptualization, investigation, methodology, and writing–review and editing. **Stefan Sunaert:** Conceptualization, formal analysis, investigation, methodology, supervision, and writing–review and editing. **Sabine Deprez:** Conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, writing–original draft, and writing–review and editing. All authors approved the final version.

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