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ORIGINAL ARTICLE

A Randomized Clinical Trial of Mindfulness-Based Stress Reduction Program Among Breast Cancer Survivors Post-Treatment: Evaluating Mediators of Cognitive Improvement

Cecile A. Lengacher, RN, PhD, FAAN, FAPOS,[1] Gizem Hueluer, PhD, Julia R. Wang, BS,[3] Richard R. Reich, PhD,[4] Hongdao Meng, MD, PhD, FGSA,[5] Jong Y. Park, MS, MPH, PhD,[4] Kevin E. Kip, PhD, FAAAS, FAHA,[6] Sandra Morgan, RN, MS,[1] Anisha Joshi, BS, BA, MS,[7] Sara Tinsley, PhD, APRN, AOCN,[4] Mahathi Krothapalli,[7] Sreenidhi Nidamanur,[8] Charles Cox, MD,[3] John Kiluk, MD, FACS,[4] Jean M. Lucas, PhD, MBA, APRN, FAAN, NEA-BC,[9] Tamela Fonseca, MSN, PhD, RN, CCRC, NE-BC,[9] Manolete S. Moscoso, PhD,[1] Elizabeth Bornstein, MSSA, LCSW, OSW-C, APHSW-C,[10] Kristine A. Donovan, PhD, MBA,[11] Lynne S. Padgett, PhD,[12] Ramya Chamkeri, BS,[8] Diya Patel, BS, BA,[8] Estella Hornback,[13] and Carmen C.S. Rodríguez, PhD, ANP-BC, AOCN[1]

Abstract

Introduction: The Mindfulness-Based Stress Reduction program for breast cancer survivors (MBSR [BCs]) is a stress-reducing program designed to increase cognitive functioning through four meditational practices. This randomized clinical trial aimed to determine if improvements in cognitive functioning and perceived cognitive abilities achieved from the MBSR(BC) were mediated through increased mindfulness, decreased rumination, and decreased perceived stress.

Methods: Breast cancer survivors (BCSs) who met inclusion criteria of stage I, II, or III BC and received either chemotherapy (CT) or both CT and radiation were randomized to either the 6-week MBSR(BC), or Breast Cancer Education Support (BCES) program, or to a usual care (UC) regimen. Analysis of covariance was first

[1]University of South Florida College of Nursing, Tampa, FL, USA.
[2]Department of Psychology, University of Bonn, Bonn, Germany.
[3]USF Morsani College of Medicine, Tampa, FL, USA.
[4]Moffitt Cancer Center, Tampa, FL, USA.
[5]School of Aging Studies, University of South Florida College of Behavioral and Community Sciences, Tampa, FL, USA.
[6]Vice President of Clinical Analytics | UPMC Health Services Division, Pittsburg, PA, USA.
[7]University of South Florida, Tampa, FL, USA.
[8]College of Arts and Sciences, University of South Florida, Tampa, FL, USA.
[9]Sarasota Memorial Health Care System, Sarasota, FL, USA.
[10]Brian D. Jellison Cancer Institute, Sarasota, FL, USA.
[11]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA.
[12]Veteran Affairs Office of Research & Development, Washington, DC, USA.
[13]FSU College of Medicine, Florida State University, Tallahassee, FL, USA.

implemented to identify potential mediators, followed by a formal mediational analysis to evaluate the effects of MBSR(BC) on 6-, 12-, and 26-week outcomes.

Results: After consent, 212 BCS were randomized to MBSR(BC) ($n = 91$), BCES ($n = 90$), or UC ($n = 31$). The mean age was 56.5 and the majority of the BCS, 73.1%, were White and non-Hispanic. Results showed increases in "observing" as part of mindfulness as a potential mediator of MBSR(BC) effects on impairments on quality of life and logical memory at 6 months relative to UC. No mediation effects were identified for outcomes measured at 6 or 12 weeks and also when MBSR(BC) was compared with the BCES program.

Discussion: These results partially supported our hypothesis that improvement in cognitive functioning would occur through increased mindfulness. Although few mediating relationships were identified, results showed a relationship between mindfulness and cognitive functioning. Both mediating relationships occurred through increases in "observing," a subconcept of "mindfulness," when compared to the MBSR(BC) with UC at 6 months. This study shows that mediators may help "optimize" clinical therapeutic treatment effects, thus contributing to the advancement of science. Trial Registration: ClinicalTrials.gov, www.ClinicalTrials.gov. Registration Number: NCT02786797.

Keywords: mediators, MBSR, mindfulness, rumination, stress

Introduction

Breast cancer is the most common cancer in women, consisting of 32% of all new female cancers projected to be diagnosed in 2024.[1] Although 90% of breast cancer survivors (BCSs) survived more than five years since diagnosis,[1] advanced treatment with chemotherapy (CT) often result in significant psychological, physical, and cognitive problems impacting their quality of life (QoL). Cognitive impairment (CI) may result in deficits in executive functioning, attention, long- and short-term memory, and language fluency, that may persist for years after treatment ends.[2] Specifically, CI impacts the QoL of BCS by decreasing processing speed,[3] attention,[4] and memory.[5,6] These cognitive deficits can persist for months, even years in some cases.[7]

Mindfulness and Cancer: Evidence shows mindfulness-based stress reduction (MBSR), a nonpharmacological stress-reducing intervention improves cancer-related symptoms.[8] Mindfulness practice is described as moment-by-moment nonjudgmental, acceptance with nonreactive awareness of internal and external experiences.[9] The theoretical biobehavioral model (Fig. 1) for this study postulates the mechanism by which the Mindfulness-Based Stress Reduction program for breast cancer survivors (MBSR[BC]) improves outcomes occurs, through increased mindfulness meditation. We propose meditation increases cognition through increased awareness and concentration through the enhancement of self-regulation of attention and acceptance resulting in improved executive functioning, working memory, and decreased negative emotional responses.[10,11]

Evidence for BCS post-CT suggests that MBSR significantly reduces feelings of stress, anxiety, and exhaustion,[8] and reduces fatigue and sleep disturbances.[12] Additionally, MBSR reduces biomarkers of inflammation,[13] salivary cortisol short-term,[14] improves sleep quality,[15] and reduces depression and fatigue in the short term.[16] As a cost-effective, practical, and safe intervention, MBSR is a recommended practice for BCS as part of the daily care routine.[17]

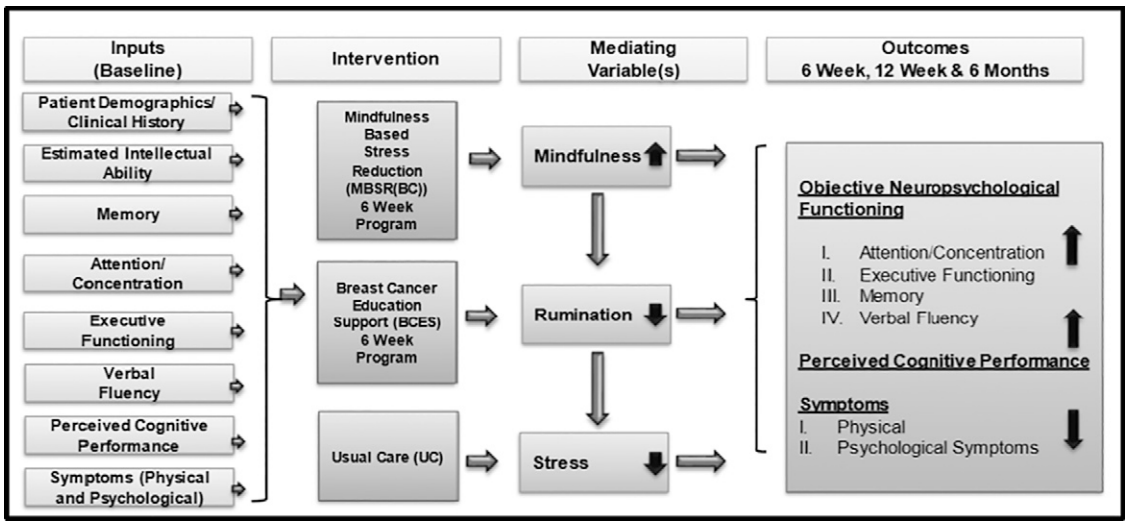

FIG. 1. The biobehavioral logic model describes the inputs (symptoms and cognitive functioning) for MBSR(BC), BCES, and usual care regimens, mediators (mindfulness, rumination, and stress) and outcomes (objective and subjective cognitive functioning) and symptoms (physical and psychological). BCES, Breast Cancer Education Support; MBSR(BC), Mindfulness-Based Stress Reduction Program for breast cancer survivors.

Mechanisms of Mindfulness: The majority of research in mindfulness among cancer survivors is devoted to testing clinical efficacy, and limited testing on elements or mechanisms of the intervention that improve outcomes.[9] Identifying the mechanisms responsible for change in the intervention may increase identifying effects at lower costs or risks.[18]

Mediators are hypothesized intermediate intervening variables that are proposed to transfer the positive cognitive and stress-reducing effects of meditation as an independent variable onto the dependent variable, or outcome.[19] Testing the mechanisms is vital to identifying how and what changes are needed for the intervention to improve effectiveness, or if the intervention did not meet expectations,[9] and evaluating if the intervention needs modification to improve outcomes.[20] Measuring the proposed mechanism/mediator at multiple time points allows for establishing if a change in the mediator precedes a change in the outcome.[18]

Our first hypothesized mediator is "mindfulness." Two major cognitive processes (awareness and attention) occur in the "healing power" of mindfulness.[21] With an increase in mindfulness, individuals may experience emotions followed by a response or adaptation which may decrease symptoms.[22] Through observing and not making judgments, one can increase emotional acceptance[23,24]; this allows for tolerating emotional experiences[25,26] and provides time to decrease reactivity and recovery from negative emotions.[27]

Our second hypothesized mediator, "rumination," is viewed as a measure of emotional regulation.[9] Rumination is defined as the tendency of neurotic, repetitive, primarily past thinking related to self-threats toward oneself.[28] Although rumination often results in a habitual mode of depression, mindfulness practice allows one to view rumination as a dysfunctional pattern, and through the practice of increased mindfulness concentration on the present moment, the spiral of negative fears and thoughts is inhibited.[9] Self-regulation of emotions and thoughts[29] reduces rumination and elaboration over the past and/or anticipated distressing experiences.[11,30]

Limited research exists on specific mediators and mechanisms of action of MBSR programs on patient outcomes. Evidence reported in a systematic review and meta-analysis shows that MBSR significantly lowered anxiety, depression, fatigue,[31] decreased stress, and greater QoL associated with increased mindfulness as a mediator.[32] Changes in cognition can be due to mediators such as mindfulness, rumination, stress, self-compassion, nonreactivity, nonjudgment, emotional regulation, and much more.[33] A meta-analysis of mediators of over 20 mindfulness-based interventions among all types of patients,[34] showed strong consistent evidence for reduced emotional reactivity as a mediator, and moderately consistent evidence supporting mindfulness, rumination, and worry as mediators. Through improved emotional regulation and mindfulness, MBSR significantly reduced mood disturbances.[33] Through the mediation of altered attention, MBSR significantly altered perception of pain[35] and reduced subjective memory impairments among BCS,[36] thus supporting MBSR for memory difficulties associated with CI.

Our previous R21 grant hypothesized that the mechanism by which MBSR(BC) was effective occurred through reductions in fear of recurrence.[37] By increases in mindfulness practice and decreases in fear of recurrence, the MBSR(BC) may modulate the hypothalamic pituitary adrenal axis and sympathetic and parasympathetic nervous system responses resulting in reduced physical, psychological, and biological markers of stress, increased QoL, and cellular immune function.[37] In this R21 MBSR(BC) study, a reduction in fear of recurrence and improvement in physical functioning mediated the improvement in perceived stress and fatigue.[37] Mediating results in a larger R01 Symptom Cluster Trial, among BCS in the MBSR(BC) showed fear of recurrence and perceived stress, and not mindfulness, mediated reductions in anxiety and fatigue at 6 and 12 weeks.[10]

This current study as the second aim of an R01 CA199160-01 cognitive clinical trial, examined the effects of the MSBR(BC) compared to the Breast Cancer Education Support (BCES) program or usual care (UC) in ameliorating CI among BCS who received CT or CT and radiation. The specific mediation aim was to "determine if improvements in objective neuropsychological functioning and perceived cognitive abilities achieved from the MBSR(BC) were mediated through increased mindfulness, decreased rumination, and decreased perceived stress." Our biobehavioral logic model (Fig. 1) describes inputs (symptoms and cognitive functions), mediators (mindfulness, rumination, and stress), outcomes (objective and subjective cognitive functioning), and symptoms (physical and psychological).

Methods

Approvals

This trial protocol was approved by the institutional review board at the University of South Florida, which also serves as the ethics committee for the University of South Florida, AdventHealth in Tampa, FL, and Sarasota Memorial Hospital, Sarasota Florida, and Moffitt Cancer Center Scientific Review Committee.

Design

Using a three-armed randomized design, BCS were randomly assigned in a 1:1:1 ratio to either: (1) the 6-week MBSR(BC); (2) the 6-week BCES program; or (3) UC. The biobehavioral logic model is displayed in Figure 1 explaining mediators and outcomes. Those blinded to the intervention assignments were the principal investigator and assessors.

Study sample

Recruitment: From October 2015 through December 2019, BCS were recruited from Moffitt Cancer Center, USF Breast Health Program, AdventHealth Tampa, Sarasota Memorial Hospital, and community groups. Data collection was completed in May 2020. Brochures and flyers designed for each recruitment site were distributed in English. Patients who expressed interest and met inclusion criteria were invited to an orientation session.

Eligibility: Women aged 21 or older were included who had: (1) a diagnosis of stage I, II, or III BC; (2) completed CT or CT and radiation, and were within 5 years post-treatment; and (3) met the screening criteria for CI through a positive response to one of two questions from the European Organization for Research and Treatment of Cancer QoL Questionnaire (EORTC-QLQ) [38]: (1) "Have you had difficulty in concentrating on things, like reading a newspaper or

watching television?" and (2) "Have you had difficulty remembering things?" BCS required the ability to read and speak English at the 8th-grade level or above. BCS with a severe current psychiatric diagnosis (e.g., bipolar disorder), Stage 0 or Stage IV BC, history of another primary cancer diagnosis with the treatment of CT and/or radiation, metastatic cancer, current neurological disorder, or a traumatic brain injury were excluded.

Randomization: Patients were randomized by use of a blocked randomly generated number scheme after the baseline assessment in a 1:1:1 ratio of one of three conditions: (1) MBSR(BC), (2) BCES, or (3) UC. Randomization was stratified by time since treatment completion, treatment regimen, and level of education. Recruitment into the UC group was capped at 30 participants due to recruitment challenges. BCS preferred the randomized assignment into the BCES program or MBSR(BC) versus the UC group due to a 26-week wait time before being offered the MBSR(BC).

Intervention procedures

MBSR(BC): The MBSR(BC) included 6 weekly, 2 h sessions, adapted by Dr. Lengacher for BCS from Dr. Kabat-Zinn's 8-week program.[39,40] The sessions were conducted by a trained psychologist and a social worker in MBSR. The MBSR(BC) consists of three elements: (1) educational materials; (2) group training and practice of four forms of meditation: sitting meditation, body scans, Gentle Hatha Yoga, and walking meditation; and (3) supportive group interaction.

BCES: BCS randomized to the BCES program attended 6 weekly, 2 h sessions that an oncology-certified registered nurse conducted. The BCES program compared to MBSR(BC) met the criteria of professional contact and group support. Time was matched equally to the MBSR(BC) and was controlled in terms of educational materials provided, supportive interaction between group members, and homework activity time. The BCES program had three similar group processes to the MBSR(BC): (1) educational material provided; (2) group discussion of educational materials and homework assignments; and (3) group processes related to sharing supportive care situations. The BCES program is based on the NIH program, "Support for People with Cancer: Taking Time Education Support Group." http://www.cancer.gov/cancertopics/takingtime/takingtime.pdf

UC: BCS in all groups continued to receive standard post-treatment medical care not modified by study participation and were asked not to initiate a mindfulness program during the study period. The BCES and UC groups were offered the MBSR(BC) within 4 – 6 months after study completion.

Data collection

Data collection intervals included four assessment time points: (1) baseline; (2) 6 weeks after intervention completion; (3) 12 weeks; (4) and 26 weeks. Expectations for MBSR(BC), BCES, and UC were provided at orientation along with obtaining informed consent. Administration of objective neuropsychological assessments and subjective cognitive, stress, and mediator surveys, clinical history, and demographic data followed orientation, 6-week, 12-week, and 26-week postassessment. MBSR(BC) and BCES participants completed an additional survey (daily diary) one time per week during the 26 weeks of data collection.

Measurements: Cognitive performance tests were selected based on previous research among cancer patients demonstrating reliability and validity with published normative data for adults.[41,42]

Objective Cognitive Performance: Memory was assessed using tests of visuospatial, verbal, and logical memory: (1)*Visuospatial memory* was measured by the Brief Visuospatial Memory Test–Revised[43]; (2)*Verbal memory* was measured by the Hopkins Verbal Learning Test–Revised[44,45]; and (3) *Logical memory* was measured by the Logical Memory I and II subscales from the Wechsler Memory Scale-IV (WMS-IV).[46] Attention/concentration was measured using the digit span subtest of the WAIS-IV, and Part 1 of the Color Trails Test (CTT-1).[47,48] Executive functioning was measured by Part 2 of the CTT-2,[47,48] Stroop Neuropsychological Screening Test.[49] Verbal fluency was measured by the Controlled Oral Word Association Test.[50] An increase in the objective cognitive performance scores is indicative of higher cognitive functioning.

Subjective Cognitive Performance: The Functional Assessment Of Cancer Therapy–Cognitive (FACT-Cog) function assessed subjective change in everyday perceived cognitive performance.[51] An increase in subjective cognitive performance is indicative of higher CI or a decrease in cognitive functioning.

Subjective Symptoms: Psychological and physical symptoms were measured by the Patient-Reported Outcomes Measurement Information System (PROMIS®) short forms for depression, anxiety, fatigue, and pain.[52] Cognitive dysfunction was assessed at recruitment by two questions from the (EORTC-QLQ).[38] Higher symptom scores indicate increased depression, anxiety, fatigue, and pain.

Standard socioeconomic demographic data including age, gender, ethnicity, highest level of education completed, marital status, income status, and employment status were collected. Clinical history data were collected on the cancer site, date and type of diagnosis, treatment, lifestyle health behaviors, and medications.

Measurements for Mediating Variables (Aim 2): The Five Facet Mindfulness Questionnaire (FFMQ) and the Cognitive and Affective Mindfulness Scare–Revised (CAMS-R) measured mindfulness; (1) FFMQ[53] measured skills of observing, describing, and acting with awareness, nonjudging, and nonreactivity to inner experience; and (2) CAMS-R[54] measured components of attention, present-focus, awareness, and acceptance. Rumination was measured by the Rumination-Reflection Questionnaire (RRQ)[28]; this assessed neurotic self-attentiveness and recurrent, primarily past-orientated thinking. The Perceived Stress Scale (PSS),[55] assessed the appraisal of life situations as "stressful." Higher scores on mindfulness indicate increased mindfulness or positive effects and higher scores for rumination and stress indicate negative effects.

Analysis plan

Statistical Analysis: Statistical analyses were conducted to evaluate whether positive effects achieved from the MBSR(BC) relative to the BCES program and UC regimen were mediated through changes in mindfulness, rumination, and perceived stress.

Analysis of covariance (ANCOVA) was initially used to examine the relationships between the MBSR(BC) intervention and potential mediators at 6 and 12 weeks (early effects) as well as 6 months (late effects). The ANCOVA models included adjustments for the baseline value of the mediator evaluated.

Mediation analyses were performed to evaluate mechanisms underlying positive effects achieved from the MBSR(BC) relative to the BCES program and UC regimen. The analyses involved two pairwise group comparisons: MBSR(BC) versus BCES and MBSR(BC) versus UC. The mediation analyses were conducted in MPlus version 8,[56] using methods described by Preacher, 1958.[57] Full information maximum likelihood estimation was used under the assumption of missingness at random and *p*-values were calculated based on a bootstrap distribution with 5,000 iterations. Full information maximum likelihood estimation is widely used to handle missing data; the advantages of this method include flexibility and the avoidance of *ad hoc* methods.[58]

Direct, indirect, and total effects were calculated according to Hicks and Tingly, 2011.[59] With this method, estimates of the total effects of the intervention on outcome variables, and indirect effects attributed to a potential mediator, were estimated. Analyses were conducted for outcomes at 6 weeks, 12 weeks, and 6 months. For the outcomes at 6 weeks, change in the mediator variables from baseline to 6 weeks was used as the mediator. For the outcomes at 12 weeks and 6 months, change in the mediator variables from baseline to 6 and 12 weeks was used as the mediator, respectively. The sequential assumption common in mediation analysis[60] was not tested because the treatment was randomized. Statistical significance was evaluated at $p < 0.05$ (two-sided). Statistical analyses were performed according to the protocol. As specified in the Aim 1 paper, the study was powered to detect a clinically meaningful effect size (between groups) of (*d*) 0.50 or greater at 80% statistical power for the main effect of MBSR(BC) on the Stroop test.[61] All participants were included in the Aim 2 analysis.

Results

Participant Characteristics: BCS (253) met inclusion criteria, resulting in 214 consenting and enrolled with a final 212 BCS randomized (after withdrawal of two BCS, before baseline assessments) to MBSR(BC) ($n = 91$), BCES ($n = 90$), or UC ($n = 31$). The total number of participants that completed all repeated assessments of the study included 72 BCS in the MBSR intervention, 70 BCS in the BCES program, and 25 in UC. BCSs were lost to follow-up in all three groups; MBSR(BC) = 10; BCES = 11; and UC = 4. Reasons included medical and family issues, work conflicts, relocation, transportation, or loss of interest. In the UC group, four lost interest and did not want to wait for the MBSR(BC) intervention.

Analyses at each time point were based on all available repeated. The majority of the BCS, 73.1%, were white and non-Hispanic, with a mean age of 56.5. Seventy-eight percent of BCS underwent CT along with radiation, while 23% only had CT in their treatment regimen. There were statistically significant differences observed at baseline between the three groups in hours worked per week, in the medical history of hysterectomy or oophorectomy, and treatment with anthracycline CT. The Consolidated Standards of Reporting Trials (CONSORT) flowchart depicting recruitment and enrollment is provided in the Aim 1 article.[61]

Effects on Outcomes: The main effects of randomized groups on outcomes across the four-time points previously have been published.[61] To summarize these results, effects on cognitive outcomes tended to be small and not statistically significant, but consistently in the hypothesized direction favoring MBSR(BC) over BCES, which was subsequently favored over UC. Larger effects were observed for symptoms, with the largest effect on fatigue. The means

Table 1. Subjective Cognition: Means and Standard Deviations by Treatment Group and Timepoint

		MBSR	*BCES*	*Control*
Measure	*Time*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*
FACT Comments from Others	Baseline	0.64 (0.81)	0.66 (0.74)	0.47 (0.72)
	6 weeks	0.41[b] (0.62)	0.51 (0.72)	0.65 (0.75)
	12 weeks	0.33[b] (0.51)	0.43 (0.61)	0.47 (0.61)
	26 weeks	0.35 (0.63)	0.45 (0.69)	0.39 (0.56)
FACT Impairments on Quality of Life	Baseline	1.58 (1.11)	1.86 (1.23)	1.56 (0.86)
	6 weeks	1.05[a] (1.04)	1.61 (1.13)	1.36 (0.98)
	12 weeks	1.00 (0.96)	1.34 (1.09)	1.22 (0.98)
	26 weeks	0.86 (0.96)	1.15 (1.14)	1.03 (1.00)
FACT Perceived Cognitive Abilities	Baseline	1.75 (0.83)	1.87 (0.79)	1.86 (0.77)
	6 weeks	1.40[a,b] (0.80)	1.66 (0.84)	1.74 (0.89)
	12 weeks	1.42 (0.81)	1.59 (0.88)	1.65 (0.88)
	26 weeks	1.30 (0.90)	1.49 (0.82)	1.51 (1.08)
FACT Perceived Cognitive Impairments	Baseline	1.88 (0.88)	1.89 (0.94)	1.69 (0.8)
	6 weeks	1.41[a,b] (0.72)	1.75 (0.89)	1.64 (0.72)
	12 weeks	1.36[a] (0.76)	1.56 (0.93)	1.47 (0.76)
	26 weeks	1.21 (0.74)	1.38 (0.83)	1.30 (0.71)

Statistical significance was tested separately at 6, 12, and 26 weeks. a = MBSR group scored significantly different than BCES group at $p < 0.05$; b = MBSR group scored significantly different than Control at $p < 0.05$.

BCES, Breast Cancer Education Support; FACT, Functional Assessment of Cancer Therapy; MBSR, Mindfulness-Based Stress Reduction Program.

Table 2. Objective Cognition: Means and Standard Deviations by Treatment Group and Timepoint

		MBSR	*BCES*	*Control*
Measure	*Time*	*Mean (SD)**	*Mean (SD)**	*Mean (SD)**
Memory				
BVMT Delayed Recall T Score	Baseline	47.45 (10.65)	46.37 (11.57)	52.23 (10)
	6 weeks	51 (11.68)	50.27 (11.21)	55.96 (7.53)
	12 weeks	51.22 (13.74)	50.71 (14.64)	53.54 (8.53)
	26 weeks	52.55 (16.81)	51.01 (14.72)	53.6 (10.67)
BVMT Total Recall T Score	Baseline	44.14 (11.9)	43.1 (11.57)	48.58 (12.19)
	6 weeks	50.58 (10.74)	49.48 (11.81)	56.31 (10.5)
	12 weeks	49.9 (13.59)	50.35 (15.51)	55.15 (9.75)
	26 weeks	51.22 (17.29)	50.1 (15.43)	52.4 (11.02)
HVLT Delayed Recall T Score	Baseline	48.14 (10.25)	47.37 (11.44)	48.32 (10.98)
	6 weeks	52.09[a] (9.12)	49.62 (11.58)	52.65 (8.68)
	12 weeks	52.94 (7.88)	48.86 (10.85)	52.31 (9.84)
	26 weeks	51.77 (8.73)	49.3 (10.95)	53.52 (10.5)
HVLT Total Recall T Score	Baseline	48.92 (9.68)	48.39 (10.35)	48.58 (12.82)
	6 weeks	51.52 (9.94)	51.89 (9.74)	52.73 (9.94)
	12 weeks	52.32 (7.79)	49.61 (10.43)	52.00 (10.90)
	26 weeks	53.7 (10.38)	52.71 (11.24)	54.64 (12.48)
WMS Logical Memory Scaled Score	Baseline	9.47 (2.98)	9.32 (2.89)	9.32 (3.18)
	6 weeks	10.61 (2.73)	10.55 (2.3)	11.15 (2.34)
	12 weeks	11.13[b] (2.44)	10.71 (2.7)	11.77 (2.44)
	26 weeks	11.03[b] (3.08)	11.16 (2.36)	12.00 (2.77)
Attention Control				
WAIS Digit Span Scaled Score	Baseline	10.56 (2.91)	10.24 (2.73)	10.74 (2.67)
	6 weeks	11.23 (3.02)	11.10 (2.83)	10.81 (3.02)
	12 weeks	11.68 (2.88)	10.86 (2.87)	11.69 (3.28)
	24 weeks	11.52 (3.23)	10.67 (2.99)	11.32 (3.02)
Color Trails T score Trial 1	Baseline	50.66 (9.08)	49.30 (8.98)	53.60 (5.52)
	6 weeks	51.77 (7.67)	51.32 (8.75)	55.73 (4.46)
	12 weeks	54.17 (11.01)	53.84 (11.67)	54.85 (5.53)
	26 weeks	57.84 (14.33)	55.67 (12.55)	56.36 (4.29)
Executive Function				
Color Trails T score Trial 2	Baseline	53.03 (10.48)	51.79 (10.91)	55.1 (7.71)
	6 weeks	54.94 (8.74)	53.21 (10.89)	56.54 (6.49)
	12 weeks	56.25 (11.33)	56.29 (13.77)	58.15 (6.03)
	24 weeks	58.94 (14.82)	57.19 (15.04)	59.24 (6.45)
Stroop Color Task Score	Baseline	111.00 (6.95)	111.81 (2.53)	111.48 (1.61)
	6 weeks	111.80 (1.16)	111.94 (0.23)	111.88 (0.59)
	12 weeks	111.46 (2.66)	111.97 (0.17)	111.96 (0.20)
	26 weeks	111.19 (5.43)	111.94 (0.29)	111.88 (0.44)
Stroop Color-Word Score	Baseline	93.08 (20.39)	92.96 (20.13)	99.42 (13.68)
	6 weeks	98.29[a] (18.56)	93.63 (20.62)	102.42 (12.22)
	12 weeks	99.44 (18.93)	97.22 (16.91)	104.00 (12.32)
	26 weeks	99.15 (19.37)	97.53 (18.67)	101.00 (17.52)
Verbal Fluency				
COWA Total	Baseline	38.53 (12.31)	35.46 (11.47)	41.23 (12.08)
	6 weeks	41.99[a,b] (11.08)	37.07 (10.23)	39.54 (10.42)
	12 weeks	43.61 (11.18)	39.06 (11.23)	42.62 (12.39)
	26 weeks	44.34 (11.8)	39.73 (11.74)	42.48 (11.15)

Statistical significance was tested separately at 6, 12, and 26 weeks controlling for baseline levels. a = MBSR group scored significantly different than BCES group at $p < 0.05$; b = MBSR group scored significantly different than Control at $p < 0.05$.

BVMT, Brief Visuospatial Memory Test; COWA, Controlled Oral Word Association; HVLT, Hopkins Verbal Learning Test; MBSR, Mindfulness-Based Stress Reduction Program; SD, standard deviation; WMS, Wechsler Memory Scale; WAIS, Wechsler Adult Intelligence Scale.

and standard deviations are shown in Table 1 (subjective cognition), Table 2 (objective cognition), and Table 3 (symptom responses).

Effects on Mediators: At 6 and 12 weeks, the MBSR(BC) group showed higher scores in the FFMQ "observing" subscale relative to the BCES group (6 weeks: $p < 0.001$; 12 weeks: $p = 0.003$). At 6 weeks, the MBSR(BC) group also showed lower scores in PSS (Perceived Stress) ($p = 0.030$) relative to the BCES group. At 6 and 12 weeks, the MBSR(BC) group showed higher scores in the FFMQ "Describing" (6 weeks: $p = 0.036$; 12 weeks: $p = 0.041$) and "Observing" (6 weeks: $p < 0.001$; 12 weeks: $p < 0.001$) subscales relative to the UC group. At 12 weeks, the MBSR(BC) group showed lower scores in the RRQ "Rumination"

Table 3. Symptom Responses: Means and Standard Deviations by Treatment Group and Timepoint

		MBSR	*BCES*	*Control*
Measure	*Time*	*Mean (SD)**	*Mean (SD)**	*Mean (SD)**
PROMIS Anxiety	Baseline	4.50 (3.65)	4.69 (3.71)	4.94 (3.78)
	6 weeks	4.01 (3.31)	4.79 (3.57)	4.50 (2.94)
	12 weeks	3.60 (3.13)	4.43 (3.47)	3.54 (2.82)
	26 weeks	3.35 (3.15)	3.83 (3.48)	3.48 (3.48)
PROMIS Depression	Baseline	2.76 (3.09)	3.31 (3.39)	3.58 (4.1)
	6 weeks	2.37 (2.97)	2.87 (3.15)	3.69 (3.74)
	12 weeks	1.89 (2.50)	2.83 (2.90)	3.46 (4.12)
	26 weeks	1.69 (2.53)	2.67 (3.13)	2.60 (3.24)
PROMIS Fatigue	Baseline	8.42 (4.24)	8.32 (4.33)	8.65 (3.77)
	6 weeks	6.10[a,b] (4.18)	8.60 (4.29)	8.00 (3.55)
	12 weeks	6.77[a] (4.28)	7.92 (4.01)	8.23 (4.04)
	26 weeks	5.22[a,b] (3.64)	6.99 (4.36)	7.64 (3.99)
Pain Interference	Baseline	10.86 (7.79)	12.26 (8.93)	11.35 (8.78)
	6 weeks	9.19 (7.87)	11.56 (7.39)	10.5 (9.19)
	12 weeks	9.64 (8.28)	12.00 (8.92)	9.80 (9.16)
	26 weeks	9.25[b] (7.81)	10.74 (8.49)	14.47 (9.51)

Statistical significance was tested separately at 6, 12, and 26 weeks controlling for baseline levels. a = MBSR group scored significantly different than BCES group at $p < 0.05$; b = MBSR group scored significantly different than Control at $p < 0.05$.

BCES, Breast Cancer Education Support; MBSR, Mindfulness-Based Stress Reduction Program; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation.

subscale ($p = 0.005$) relative to the UC group. At 6 months, the MBSR(BC) group showed higher scores in the FFMQ "Describing" ($p = 0.001$) and "Observing" ($p = 0.012$) subscales and the CAMS-R "Awareness" subscale ($p = 0.024$) relative to the UC group. There were no significant differences relative to the BCES group at 6 months.

Mediation Results: Significant indirect effects were found for the "Observing" subscale of the FFMQ when comparing the MBSR(BC) group with the UC group at 6 months and when the "Impairments on the QoL" subscale of FACT (Fig. 2) and the WMS-IV "Logical Memory" score (Fig. 3) were the outcomes, respectively.

Relative to the UC group, the MBSR(BC) group showed more increase in the "observing" subscale from baseline to 12 weeks (a = 3.33, SE = 0.95, $p < 0.01$), which was in turn related to lower levels of "Impairments on QoL" at 6 months (b = −0.05, SE = 0.02, $p = 0.02$). This resulted in an indirect effect of (ind = −0.17, SE = 0.09, $p = 0.04$). However, the total effect was not significant (tot = −0.16, SE = 0.23, $p = 0.48$), indicating that participants in the MBSR(BC) group showed lower levels of "Impairments on QoL" at 6 months relative to the UC group only if they increased in "observing" from baseline to 12 weeks.

With the WMS logical memory score as the outcome, the MBSR(BC) group showed more increase than the UC group in the "Observing" subscale from baseline to 12 weeks (a = 3.36, SE = 0.96, $p < 0.001$), which was in turn related to higher levels of "logical memory" at 6 months (b = 0.19, SE = 0.07, $p < 0.01$). This resulted in an indirect effect of (ind = 0.64, SE = 0.29, $p = 0.026$). However, the total effect was not significant (tot = −1.00, SE = 0.66, $p = 0.134$), indicating that participants in the MBSR(BC) group showed higher levels of logical memory at 6 months relative to the UC group only if they increased in "Observing" from baseline to 12 weeks. No significant indirect effects were found for other outcomes and mediators at 6 weeks, 12 weeks, and 6 months and when comparing the MBSR(BC) group with the BCES group.

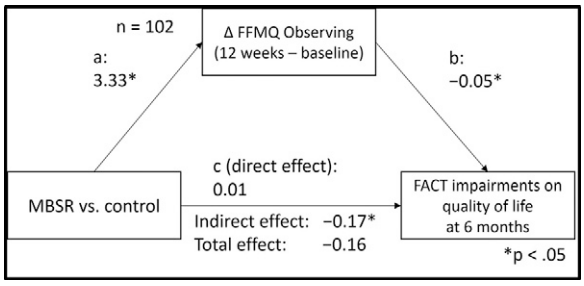

FIG. 2. The role of FFMQ (observing) as a mediator for the effect of MBSR(BC) on FACT impairments on quality of life relative to UC at 6 months. FFMQ, Five Facet Mindfulness Questionnaire; MBSR(BC), Mindfulness-Based Stress Reduction Program for breast cancer survivors; FACT, Functional Assessment of Cancer Therapy; UC, usual care.

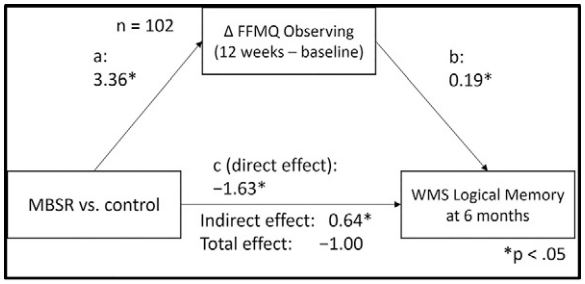

FIG. 3. The role of FFMQ (observing) as a mediator for the effect of MBSR(BC) on logical memory relative to UC at 6 months. MBSR(BC), Mindfulness-Based Stress Reduction Program for breast cancer survivors; FFMQ, Five Facet Mindfulness Questionnaire; UC, usual care.

Discussion

The goal of this mediation research was to provide new knowledge and evidence identifying potential mechanisms of action for the MBSR(BC) intervention among BCS who completed CT or CT and radiation treatment. After initial analyses of early (baseline to 6 and 12 weeks, respectively) and late (baseline to 6 months) intervention effects of MBSR(BC) relative to the BCES program or a UC regimen, results pointed to increases in observing as part of mindfulness as a potential mediator of MBSR(BC) effects on impairments on QoL and logical memory at 6 months relative to UC. The MBSR(BC) group did not differ from UC in terms of impairments on QoL at 6 months; however, the mediation effects indicated that the MBSR(BC) was associated with an increase in observing from baseline to 12 weeks relative to UC, which was in turn associated with lower levels of impairments on QoL at 6 months. Unexpectedly, the MBSR(BC) group scored lower on a test of logical memory relative to UC at 6 months. However, the mediation effect indicated that the MBSR(BC) was associated with an increase in observing from baseline to 12 weeks relative to UC, which was in turn associated with higher levels of logical memory at 6 months. Rumination, perceived stress, and subconcepts of mindfulness other than observing were not identified as mediators. No mediation mechanisms were identified for outcomes at 6 and 12 weeks. Also, no mediation mechanisms were identified for differences between the MBSR(BC) and the BCES program. Potential bias was a consideration in this study. Randomization, corrected for selection bias and performance bias related to prior use of techniques similar to MBSR was assessed at baseline. Results showed all three groups were similar in their experience. Detection bias was corrected by randomization that minimized differences in characteristics. Additionally, attrition bias was corrected by including all data from four time points in the analyses, even if not complete.

The improvements in objective neuropsychological functioning, such as logical memory, and perceived cognitive abilities in the MBSR(BC) group are consistent with current literature on increased mindfulness as a mediator.[9] Increased mindfulness is achieved through awareness and attention, or the observation of one's internal and external world, this was emphasized in the MBSR(BC).

The reduction of "impairments on QoL" was indirectly affected, or mediated, by mindfulness. Participants only showed a reduction in Impairments in QoL relative to UC if they showed an increase in "Observing" from baseline. Similarly, participants only showed an increased logical memory after 6 months if they showed an increase in mindfulness "Observing" from baseline.

The MBSR(BC) group showed reduced perceived stress at 12 weeks relative to BCES. Lower rumination, higher describing, observing, and awareness were observed in the MBSR(BC) group relative to UC, but only observing as a part of mindfulness was determined to have an indirect mediation effect upon outcomes of impairments of QoL. Previous findings indicate the reduction in pain may be related to an altered perception of pain,[35] and the reduction in fatigue may be related to increased mindfulness[31]; however, we were unable to find a mediator related to the reduction of pain. The mediating relationships through the mechanisms of "observing" as related to mindfulness have only been tested among BCS and may be generalizable to the understanding and further knowledge development of the mediation effects of MBSR(BC) on other types of cancer survivors or among individuals with chronic health conditions.

Limitations: In summary, there were a few limitations to our study. Although the selection of mediators and outcomes was guided by our hypothesized mechanism of how we proposed MBSR(BC) would increase cognitive functioning, and although rumination and stress were affected, they did not have a direct mediating effect on the outcomes. Additionally, the UC group was relatively small compared with the MBSR(BC) and BCES groups, which may have resulted in less power to detect differences relative to the UC group. Some of the early effects on mediators and outcomes did not persist at 6 months, which may be due to a lack of adherence after the intervention ended. Future larger studies should continue to determine if these mediation effects can be replicated.

Conclusions: This R01 study contributes to the advancement of the scientific understanding of the mechanism of action of the MBSR(BC) "cognitive adapted program" for advanced stage BCS who may have decreased cognitive functioning due to chemo brain. Although the efficacy of MBSR is well established, less is known regarding the mechanisms through which MBSR achieves its psychological and physical effects. There continues to be limited research focused on investigating other cognitive mechanisms through which the MBSR(BC) achieves physical and psychological effects. Since the MBSR(BC) is believed to be a self-regulating intervention allowing for emotional and cognitive control, testing specific mediators leading to improved memory and cognitive functioning among chemobrain BCS was a vital consideration for these BCS.

Related to our hypotheses, only two mediating relationships were identified related to cognitive functioning—both were through increases in mindfulness through the mechanism, of "observing" a subconcept of mindfulness when comparing the MBSR(BC) with UC at 6 months. Related to our model, although our results did not find rumination and stress as having a mediating relationship, the results showed that the MBSR(BC) group had lower rumination, higher describing, observing, and awareness relative to UC, with only "observing" as a subconcept of mindfulness showed an indirect mediation effect upon outcomes of "Impairments of QoL." By testing the mechanisms of the program, this study also contributes to the improvement and advancement of nonpharmacological treatment for cancer survivors showing that it may "optimize" the clinical therapeutic treatment effects of MBSR on multiple distressing symptoms. It was also interesting that mediation effects were found at 26 weeks, but not earlier. This may indicate that a sufficient number of time points is needed to determine the shape and temporal sequencing of change.

Data Sharing Statement

Data will be made available to faculty researchers at universities in the United States through a data sharing agreement and to approved members of the scientific community 3 years after the final grant completion date. This dissemination plan will undergo yearly review. Pending results, effective intervention materials, and programs will be shared through a website or national repository.

Authors' Contributions

C.A.L. initiated the development of the program research objectives, designed the programs, and applied for funding as the principal investigator in the study. G.H., K.E.K., R.R.R., and H.M. were responsible for the methodology and data curation. M.S.M. and E.B. contributed to the delivery of the mindfulness intervention, while C.C.S.R. contributed to the delivery of the BCS educational program. K.A.D. was the site principal investigator for Moffitt Cancer Center. T.F. was the site coordinator for Sarasota Memorial Health Care System and J.M.L. was the site principal investigator for Sarasota Memorial Health Care System. C.C. and J.K. assisted with identifying patients for study recruitment. C.A.L. was the creator of the protocol article with contributions from R.R.R. and J.Y.P. All authors including, J.R.W., S.M., A.J., S.T., S.N., M.K., L.S.P., R.C., D.P., and E.H. contributed to multiple revisions of the article and approved the final edited version to be published.

Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Gizem Hueluer, PhD
University of Bonn
Department of Psychology
Kaiser-Karl-Ring 9
53111 Bonn
Germany

E-mail: ghueluer@uni-bonn.de