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ORIGINAL ARTICLE

Efficacy of Mindfulness-Based Stress Reduction for Breast Cancer (MBSR(BC)) a Treatment for Cancer-related Cognitive Impairment (CRCI): A Randomized Controlled Trial

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Abstract

Introduction: The Mindfulness-Based Stress Reduction (MBSR) Program for breast cancer survivors (BCS) is designed to enhance cognitive training through formal and informal meditational practices. This randomized clinical trial (RCT) aimed to evaluate if BCS assigned to either the MBSR(BC), Breast Cancer Education Support (BCES), or Usual Care (UC) regimens experienced greater improvements at 6, 12, and 26 weeks on objective and subjective cognitive performance.

Methods: BCS ($n = 212$) randomized to a three-group RCT: MBSR(BC) ($n = 91$), BCES ($n = 90$), or UC ($n = 31$) were assessed on cognitive performance and symptoms at baseline, 6, 12, and 26 weeks. Linear mixed models were fit to evaluate the effects of the MBSR(BC) program, hypothesizing ordered effect improvements: (MBSR[BC] highest, BCES intermediate, UC lowest) along with baseline characteristics evaluated as moderators.

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Results: Of the BCS (mean age of 57), 73% were White, and non-Hispanic, and 77% received both chemotherapy (CT) and radiation. Cognitive performance improved in all groups. Although there were no statistically significant between-group differences in cognitive outcomes, significant symptom reductions occurred for the MBSR(BC) group ($p = 0.003$). Within-group effect size analysis at 26 weeks showed substantial improvements in all three groups (effect sizes >0.50) in subjective impairments and quality of life (effect size >0.50) and objective measures of cognitive performance. MBSR(BC) showed the largest within-group effect size in the reduction of fatigue (effect size = 0.81). Effect sizes occurred in the hypothesized direction for 10 of the 18 outcomes.

Discussion: Although the MBSR(BC) program did not show significant differences in cognitive performance compared with BCES and UC, all groups improved and reductions in fatigue were beneficial for MBSR(BC). Results suggest that cognitive performance may improve after CT over time considering one's natural history. Furthermore, BCS enrolled in RCTs may be more motivated to improve their health status (NCT02786797).

Keywords: cancer, cognitive function, MBSR, integrative medicine, RCT

Introduction

Cancer-related cognitive impairment (CRCI) among breast cancer survivors (BCS) is a common distressing long-term side effect after receiving chemotherapy (CT) or radiation.[1] Specific causes of CRCI and treatment effects continue to remain unclear.[1] Chemotherapy improves the 15-year survival rate[2]; however, chemotherapy-associated cognitive dysfunction or "chemo brain" affects 20%–90% of BCS[3] years after treatment ends.[4–10] Similarly, BCS treated with radiation therapy often report cognitive impairment.[11,12]

BCS report multiple cognitive domains affected as follows: loss in short-term and long-term memory, executive functioning, processing speed, visual, spatial, and constructional ability, and decreased attention and concentration.[7,8,13–19] Cognitive impairment (CI) negatively impacts quality of life,[20,21] ability to concentrate,[22] and work,[23] contributing to increased economic burdens and psychological stress.[14,18,24–27] CI is a significant problem with an increase in the number of female invasive BC cases estimated to be 310,720 in 2024.[28]

Given that pharmacologic treatment for CI may not be optimal during treatment,[29] the National Comprehensive Cancer Network recommends the use of nonpharmacologic interventions.[30] Limited research exists on testing the effects of integrative approaches on CI and examining if CI is associated with psychological distress.[7]

Mindfulness-Based Stress Reduction (MBSR) is postulated to improve cognition through the mechanism of increased mindfulness occurring during the practice of meditation by learning as follows: (1) "sustained attention" to each moment; (2) attention switching between thoughts and feelings[31]; and (3) nonelaborative awareness[32] by changing negative context of experiences.[33] Our MBSR program for BCS, MBSR(BC) is postulated to interrupt the stress response by increasing attention and reappraising the situation as less threatening, thus decreasing negative emotional responses.[31] Mindfulness meditation (MM) practice improves executive functioning by enhancing skills in self-regulation of attention and acceptance, resulting in improved working memory.[32,34–36]

Current evidence remains sparse on testing the effects of MBSR on cognition among BCS. A pilot MBSR study examining CRCI among BCS and colorectal patients randomized patients to MBSR ($n = 35$) or a Fatigue Education and Support (ES) ($n = 36$) program.[37] MBSR participants improved significantly on "attention" compared with ES, with executive functioning sustained for the MBSR group.[37] Our MBSR(BC) program compared with Usual Care (UC) improved BCS's psychological and physical symptoms, quality of life (QOL),[38,39] symptom clusters,[40,41] and subjective cognitive performance.[42]

A systematic review of MBSR interventions and cognitive functioning among BCS[43] reported six MBSR studies with the following: (1) no improvements in cognitive functioning for two studies[41,44]; (2) subjective cognitive improvements in a mindfulness clinic program for cancer survivors,[45] and among BCS attending an MBSR program compared with a control[46]; and (3) improved cognition in a mindfulness group compared with metacognition and control,[47] and the above Johns (2016) study reports sustained improvements at 6 months.[37] A recent (2022) study among BCS randomized to MBSR ($n = 30$) compared with a waitlist control group ($n = 30$) reported significant reductions in subjective memory failure, in the MBSR group.[48]

Mindfulness offers a solution to mitigate CI by interrupting the stress response.[33] Mindfulness practice potentially improves executive functioning[31] through self-regulation of awareness, attention, concentration, and acceptance, resulting in improved memory.[32,34–36] Despite the magnitude of the problem, gaps in knowledge also remain related to the variability in objective and subjective cognitive measurements, use of multiple study designs, and lack of clinical trial evidence on pre-existing CI.

In summary, although studies of MBSR among BCS have reported improvements in multiple psychological and physical symptoms and subjective cognitive performance, few randomized clinical trials (RCTs) test the effects of MBSR on objective cognitive performance after chemotherapy. Therefore, the major aim of this trial was to evaluate if BCS assigned to the MBSR(BC), Breast Cancer Education Support (BCES), or UC regimens experienced greater improvements at 6, 12, and 26 weeks on objective and subjective measures of cognitive performance. We hypothesized that cognitive improvement would be greatest first for MBSR(BC), followed by BCES, and lowest in the UC group across the 26 weeks.

Methods

Participants

Recruitment occurred from October 2015 to July 2020 and, due to COVID, was not complete until 2022. BCS (253)

who met the inclusion criteria (age 21 or older, with a diagnosis of Stage I, II, or III BC, who completed CT or CT/radiation within 5 years and met screening criteria) were recruited from Moffitt Cancer Center, USF Morsani Center for Advanced Healthcare, AdventHealth in Tampa, FL, and Sarasota Memorial Health Care System, Sarasota Florida. Exclusion criteria included a severe psychiatric diagnosis, Stage 0 or Stage IV BC, a second cancer diagnosis treated with CT and/or radiation, a neurologic disorder, or a traumatic brain injury.

Procedures

Study design and randomization. A total of 212 BCS out of 214 BCS consented and were randomly assigned in a 1:1:1 ratio to the following: (1) a 6-week MBSR(BC) program, (2) a 6-week BCES program, or (3) UC.

A SAS (v. 9.3 SAS Institute, 2015) macro created a stratified block randomization scheme stratifying BCS by time since treatment completion, treatment regimen (CT or CT and radiation), and level of education. The statistician first prepared the randomization list using ID numbers identified by the program manager, then assigned participants to a group, and placed assignments in a sealed envelope. Upon participant completion of informed consent and baseline assessments, the envelope was opened by the participant to reveal their assignment. Once UC reached 30 subjects, the blocked randomly generated scheme occurred in a 1:1 ratio of one of two conditions as follows: (1) MBSR(BC) or (2) BCES. The Principal Investigator and assessors were blinded to the intervention assignments. The sample size was calculated to detect a clinically meaningful effect size (between groups) of *(d)* $\sim$0.5 or greater at 90% statistical power. This trial is registered under ClinicalTrials.gov, www.ClinicalTrials.gov Registration Number: ClinicalTrials.gov Identifier: NCT02786797.

Recruitment and data collection procedures. This trial was approved by the Institutional Review Board at the University of South Florida, Moffitt Cancer Center's Scientific Review Committee, AdventHealth, and Sarasota Memorial Health Care System. BCS meeting inclusion criteria provided informed consent, followed by obtaining baseline assessments and randomization to MBSR(BC), BCES, or UC.

Intervention procedures: MBSR(BC). BCS assigned to MBSR(BC) attended six weekly, 2-h sessions conducted by a psychologist and social worker trained in MBSR. Dr. Lengacher received training in Dr. Kabat-Zinn's 8-week program[31] and adapted the 8 weeks to 6 weeks for BCS.[39] The MBSR(BC) program enhanced mindfulness cognitive training in self-regulation of awareness, attention, and concentration through the following: (1) educational materials; (2) formal meditation practice in sitting meditation, body scan, Gentle Hatha Yoga, and walking meditation; (3) informal meditation in everyday life; and (4) group supportive interaction. BCS practiced MM techniques 15–45 min per day and recorded practice time. A manual and Compact Discs were provided to the MBSR(BC) group.

Intervention procedures: BCES. BCS in the BCES program attended six weekly, 2-h sessions conducted by an oncology-certified nurse. The BCES program was matched to MBSR(BC) on the following: (1) educational materials; (2) group discussion and homework; and (3) group supportive interaction and recorded feelings and coping mechanisms in a daily diary (matched with MBSR). The BCES program designed by Dr. Lengacher was based on the NCI program, "Support for People with Cancer: Taking Time" (https://www.cancer.gov/publications/patient-education/takingtime.pdf). A BCES manual was provided, and the MBSR(BC) program was offered upon study completion.

Fidelity. A structured observational method, including a time-sequenced evaluation of instructor adherence to the MBSR(BC) and BCES protocol, was completed by a research assistant for each group. Instructor's adherence was evaluated monthly for fidelity to the MBSR(BC) and BCES time sequence delivery in the interventions.

UC. BCS assigned to the UC group received standard post-treatment care and were asked not to initiate a mindfulness program during the study period. At study completion, they were offered the MBSR(BC) program.

Measurements

Objective cognitive performance. Cognitive performance tests selected were based on research among cancer patients[49,50] and demonstrated reliability and validity among adults.[49,50] Intellectual ability was measured at baseline by the Wechsler Test of Adult Reading.[51] The following neuropsychological tests were conducted at baseline, 6, 12, and 26 weeks. Memory was assessed by the following three measures: (1) *Visuospatial memory,* the Brief Visuospatial Memory Test–Revised (BVMT-R)[52]; (2) *Verbal memory*, the Hopkins Verbal Learning Test–Revised (HVLT-R)[53,54]; and (3) *Logical memory*, the Logical Memory I and II with the Wechsler Memory Scale-IV (WMS-IV).[55]

Attention/Concentration was assessed by the Digit Span subtest of the Wechsler Adult Intelligence Scale, Fourth Edition and Part 1 of the Color Trails Test (CTT-1).[56,57] Executive functioning was assessed by Part 2 of the Color Trails Test (CTT-2)[56,57] and Stroop Neuropsychological Screening Test (SNST).[58] Verbal fluency was assessed by the Controlled Oral Word Association Test.[59]

Subjective cognitive performance. The Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog) assessed subjective cognitive performance.[60] Psychological and physical symptoms were measured by the PROMIS® (Patient-Reported Outcomes Measurement Information System) short forms for Depression, Anxiety, Fatigue, and Pain.[61] Cognitive dysfunction was assessed at recruitment by two questions from the European Organization for Research and Treatment of Cancer Quality of Life questionnaire.[62]

Demographic and clinical history. Standard socioeconomic demographic data, including age, gender, ethnicity, education, marital, income, and employment status, were collected at baseline, including a clinical history and lifestyle health behaviors.

Statistical methods

Statistical data analysis plan. Participants were randomly assigned to conditions, thus minimizing bias and differences in characteristics between participants. Baseline demographic and clinical characteristics were presented by random assignment as the mean and standard deviation for continuous variables and counts and percentages for categorical variables. Raw scores on objective cognitive tests were converted into standardized scores by age and education-matched norms, demonstrated in prior research.[63] This trial used a 3-group (MBSR[BC] vs. BCES versus UC) × 4 (time points) mixed model design. This trial was conducted using the "intention to treat" power calculation for the number of subjects required to detect a clinically meaningful effect size of ∼0.50 with MBSR(BC) for executive functioning (primary outcome). Standardized effect sizes (*d*) were used to describe between-group differences in outcome measures at each time point. A sample of 300 participants (with a minimum of 250 expected to complete and a maximum dropout rate of 17%) was selected to conduct a rigorous evaluation of the efficacy of MSBR(BC). A sample of 110 per MBSR(BC) and 110 per BCES with 30 per UC group (total $n = 250$) provided 80% power to detect a clinically meaningful effect size (defined as ∼0.50) of 0.47 for the Stroop Test (SNST) (a primary outcome measure). Other outcome variables included objective and subjective cognitive measures and measures of psychological and physical symptoms. SAS System, version 9.4 was implemented to calculate sample size and power calculations. To statistically test the pattern of between-group effects, the use of random effects (mixed) models for continuous outcomes[64] allowed for the inclusion of subjects with missing data and accommodated the nominal baseline differences in the dependent variable being modeled. Inclusion of participants with missing data corrected for "attrition bias" was done by including participants with any follow-up data corrected for "attrition bias" even if they did not complete all three time points. To minimize comparisons, outcome measures were tested with a linear mixed model using an order-restricted approach with MBSR(BC) hypothesized *first* to show the greatest improvement, followed by BCES and UC. The only *p*-value evaluated and reported was the 4-time point slope (rate of improvement over all follow-up time) at 26 weeks. For the mixed model analyses, an unstructured covariance matrix was specified, and in secondary analyses, within-group effect sizes from baseline to 26 weeks were calculated.

Moderator effects were explored as tests of interaction effects in the context of linear mixed models and by calculation of effect sizes within stratified analyses. Baseline characteristics evaluated as moderators on cognitive improvement included the following: type of chemotherapy, radiation, time

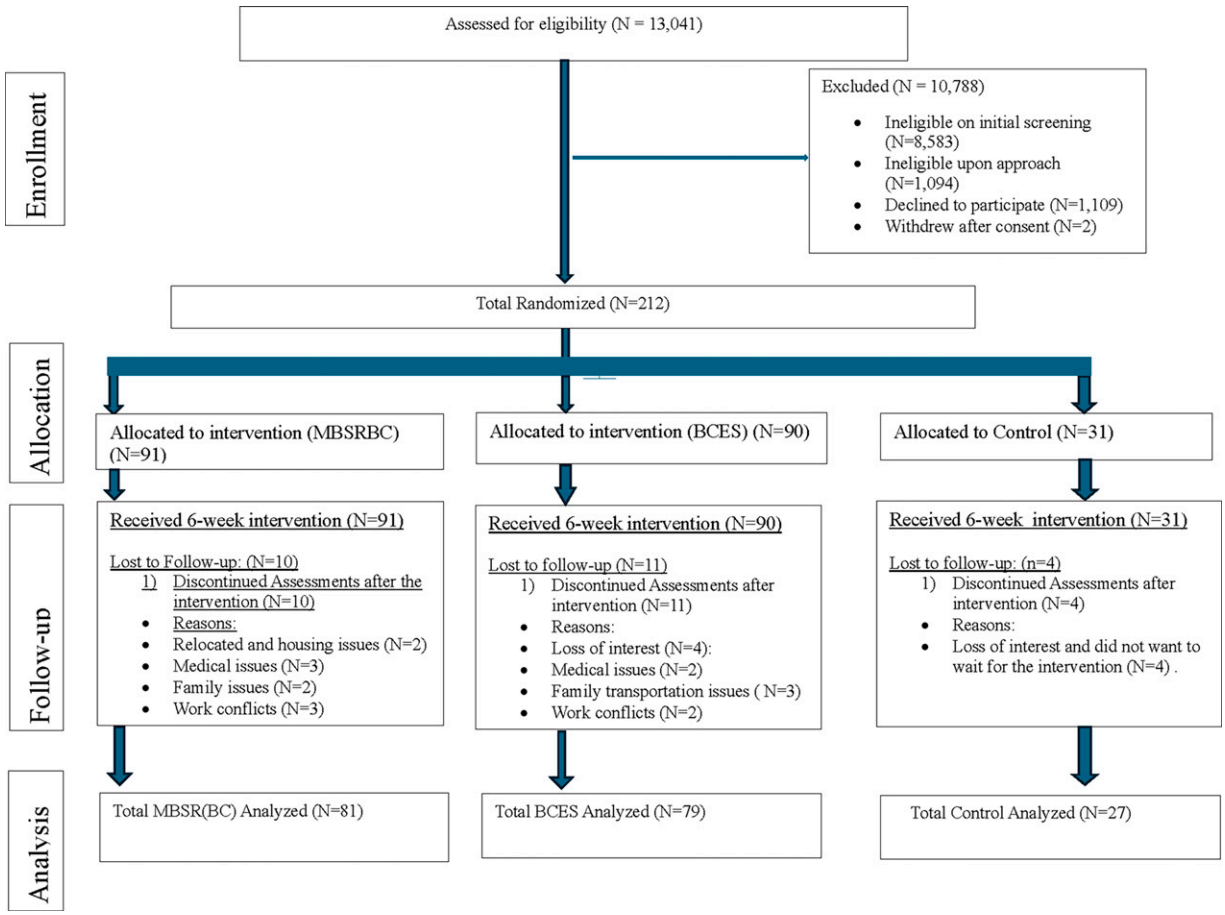

FIG. 1. CONSORT flowchart depicting the recruitment and enrollment (214 consented, with 2 withdrawing before baseline assessments) resulted in 212 randomly assigned to the Mindfulness-Based Stress Reduction (MBSR) intervention, Breast Cancer Education Support (BCES) intervention, or Usual Care (UC).

since treatment, and formal and informal practice of MBSR(BC).

Only the BCES and MBSR(BC) groups were included due to the small sample size for the UC group.

Missing data. Less than 10% of outcome data were missing. Maximum likelihood estimation was used to create unbiased parameter estimates without the need for multiple imputations.

Results

Participant characteristics

Out of 214 BCS who consented and enrolled, 2 withdrew prior to the completion of baseline assessments. Thus, 212 BCS who completed baseline assessments were randomized to MBSR(BC) ($n = 91$), BCES ($n = 90$), or UC ($n = 31$). The CONSORT diagram in Figure 1 identifies the number of BCS screened, enrolled, and randomized. Table 1 lists the demographic characteristics by random assignment showing a mean age of 56.5 and a majority or 73% White, non-Hispanic. Table 2 shows that BCS completed CT more than a year previous to enrollment, and most (77%) received CT and radiation. Baseline demographic and clinical characteristics were similar by random assignment, although it appeared that the MBSR(BC) group was more likely to have received anthracycline CT.

Compliance

Median reported "formal" practice time for MBSR(BC) was 87.8 h over 26 weeks (3.9 h per week), with 75% reporting practicing at 2,500 min (41.7 h) over the 26 weeks. Median reported "informal" practice time over 26 weeks was 2,627 min (1.7 h per week) compared with the median weekly "formal" practice time of 2,646 min (1.7 h per week).

Efficacy of MBSR(BC) compared with BCES and UC on objective cognitive outcomes

For the five objective cognitive measures, including our primary outcome the Stroop Color Task, between-group effect sizes were small (<0.50) and not statistically significant over time (Table 3). Both the Stroop Color Task and Stroop Color Word executive function measures were similar by random assignment, with all three groups improving from baseline. Although between-group comparison of the Logical Memory Scaled Score was statistically significant ($p = 0.02$), the change scores were best for the UC group followed by the BCES group and then the MBSR(BC) group (i.e., opposite the hypothesized direction). The two objective

Table 1. Demographic Characteristics by Random Assignment

Characteristic	*Total* (n = 212)	*MBSR* (n = 91)	*BCES* (n = 90)	*Control* (n = 31)
Age, mean, SD	56.5, 10.7	56.3, 11.4	55.4, 9.7	59.5, 11.0
Race/ethnicity, %				
White, non-Hispanic	73.1 (155)	75.8 (69)	68.9 (62)	77.4 (24)
White, Hispanic	10.8 (23)	7.7 (7)	14.4 (13)	9.7 (3)
Black, non-Hispanic	11.3 (24)	14.3 (13)	7.8 (7)	12.9 (4)
Black, Hispanic	0.5 (1)	0.0 (0)	1.1 (1)	0.0 (0)
Other/Unknown	4.2 (9)	2.2 (2)	7.8 (7)	0.0 (0)
Educational attainment, %				
Less than a college degree	21.8 (46)	24.2 (22)	18.0 (16)	25.8 (8)
Some college or AA degree	28.4 (61)	26.4 (24)	32.6 (30)	22.6 (7)
College degree	25.1 (53)	24.2 (22)	22.5 (20)	35.5 (11)
Graduate/professional school	24.6 (52)	25.3 (23)	27.0 (24)	16.1 (5)
Employment status, %				
Employed >=32 h/week	29.9 (64)	35.2 (32)	28.1 (26)	19.4 (6)
Employed <32 h/week	15.6 (33)	11.0 (10)	24.7 (22)	3.2 (1)
Retired	26.1 (55)	28.6 (26)	22.5 (20)	29.0 (9)
Other	28.4 (60)	25.3 (23)	24.7 (22)	48.4 (15)
Annual income, %				
Less than $10,000	11.8 (25)	6.8 (6)	13.1 (12)	22.6 (7)
$10,000 to < $20,000	12.8 (27)	10.2 (9)	17.9 (16)	6.5 (2)
$20,000 to < $40,000	22.7 (48)	22.7 (21)	21.4 (19)	25.8 (8)
$40,000 to < $80,000	27.1 (57)	30.7 (28)	26.2 (24)	19.4 (6)
$80,000 to < $100,000	7.9 (17)	10.2 (9)	3.6 (3)	12.9 (4)
$100,000 or more	17.7 (38)	19.3 (18)	17.9 (16)	12.9 (4)
Marital status, %				
Married	62.6 (133)	62.6 (57)	61.8 (56)	64.5 (20)
Single	11.8 (25)	12.1 (11)	12.4 (11)	9.7 (3)
Widowed	3.8 (8)	4.4 (4)	4.5 (4)	0.0 (0)
Divorced	20.4 (43)	18.7 (17)	20.2 (18)	25.8 (8)
Other	1.4 (3)	2.2 (2)	1.1 (1)	0.0 (0)

MBSR, Mindfulness-Based Stress Reduction; BCES, breast cancer education support; SD, standard deviation.

Table 2. Clinical and Behavioral Characteristics by Random Assignment

Characteristic	*Total* (n = 212)	*MBSR* (n = *91*)	*BCES* (n = *90*)	*Control* (n = *31*)
Chemotherapy regimen, %				
Chemotherapy alone	22.6 (48)	20.9 (19)	21.1 (19)	32.3 (10)
Chemotherapy plus radiation	77.4 (164)	79.1 (72)	78.9 (71)	67.7 (21)
Type of chemotherapy, %				
Anthracycline	44.8 (95)	54.9 (50)	37.8 (34)	35.5 (11)
Taxane	97.2 (206)	97.8 (89)	96.7 (87)	96.8 (30)
Platinum	26.9 (57)	24.2 (22)	32.3 (29)	19.4 (6)
Cytoxan	67.5 (143)	71.4 (65)	62.2 (56)	71.0 (22)
Time since treatment completion, %				
1 year or less	33.5 (71)	30.8 (28)	34.4 (31)	38.7 (12)
More than 1 year	66.5 (141)	69.2 (147)	65.6 (59)	61.3 (19)
Breast cancer type, %				
Lobular carcinoma	6.6 (14)	5.5 (5)	8.9 (8)	3.2 (1)
Ductal carcinoma	26.4 (56)	25.3 (23)	28.9 (26)	22.6 (7)
Invasive lobular	6.1 (13)	2.2 (2)	7.8 (7)	12.9 (4)
Invasive ductal	33.0 (70)	38.5 (35)	32.2 (29)	19.4 (6)
Other/unknown	27.8 (59)	28.6 (26)	22.2 (20)	41.9 (13)
Breast cancer side, %				
Left	45.3 (96)	46.2 (42)	48.9 (44)	32.3 (10)
Right	40.6 (86)	40.7 (37)	37.8 (34)	48.4 (15)
Both	6.6 (14)	3.3 (3)	7.8 (7)	12.9 (4)
Unknown	7.5 (16)	9.9 (9)	5.6 (5)	6.5 (2)
Other cancer history, %				
No	88.8 (188)	85.4 (78)	92.0 (83)	83.9 (26)
Yes	11.2 (24)	14.6 (13)	8.0 (7)	9.7 (3)
Unknown	0.0 (0)	0.0 (0)	0.0 (0)	6.5 (2)
Medical history, %				
Vascular issue	6.6 (14)	7.7 (7)	5.6 (5)	6.5 (2)
Respiratory issue	10.9 (23)	15.4 (14)	9.0 (8)	3.2 (1)
Hysterectomy	32.5 (69)	41.8 (38)	26.1 (24)	22.6 (7)
Oophorectomy	31.0 (66)	42.4 (39)	21.8 (20)	25.8 (8)
Family history of breast cancer, %				
No	67.7 (144)	52.7 (48)	73.5 (66)	60.0 (19)
Yes	32.3 (68)	28.6 (26)	26.5 (24)	40.0 (12)
Unknown	0.0 (0)	18.7 (17)	0.0 (0)	0.0 (0)
Behavioral factors, %				
Cigarette use				
Current	5.2 (11)	3.3 (3)	7.9 (7)	3.2 (1)
Former	27.5 (58)	29.7 (27)	24.7 (22)	29.0 (9)
Never	67.3 (143)	67.0 (61)	67.4 (61)	67.7 (21)
Alcohol use	61.9 (131)	61.5 (56)	61.4 (55)	64.5 (20)
Caffeinated beverage use	61.9 (131)	61.5 (56)	61.4 (55)	64.5 (20)
Exercise, %				
0–1 day/week	28.3 (60)	29.7 (27)	26.7 (24)	29.0 (9)
2–4 days/week	42.9 (91)	38.5 (35)	47.8 (43)	41.9 (13)
5–7 days/week	28.8 (61)	31.9 (29)	25.6 (23)	29.0 (9)
Regular use of social therapy	76.9 (163)	74.7 (68)	76.7 (69)	83.9 (26)

MBSR, Mindfulness-Based Stress Reduction; BCES, breast cancer education support; SD, standard deviation.

measures of attention control showed small, nonsignificant between-group effect sizes over the 26 weeks with all three groups improving from baseline. Similar results were observed for verbal fluency.

Efficacy of MBSR(BC) compared with BCES and UC on subjective cognitive outcomes

In pairwise between-group comparisons, effect sizes (*d*) for the four subjective measures of cognitive performance were small (<0.50) and not statistically different by random assignment (Table 4). Mean values for all subjective cognitive measures other than the FACT "Comments From Others" improved over time in all three groups.

Efficacy of MBSR(BC) compared with BCES and UC on psychological and physical symptoms

For secondary symptom outcomes, all three groups showed reductions in anxiety, depression, and fatigue over

Table 3. Objective Cognition: Means and Standard Deviations (SD) by Treatment Group and Time point; Pairwise Effect Sizes and *P*-Values

		MBSR	*BCES*	*Control*	*MBSR vs. Control*	*BCES vs. Control*	*MBSR vs. BCES*	
Memory	*Time*	*Mean (SD)*[a]	*Mean (SD)*[a]	*Mean (SD)*[a]	*d (se)*[b]	*d (se)*[b]	*d (se)*[b]	p-Value*
BVMT Delayed Recall T Score	Baseline	47.4 (10.6)	46.4 (11.6)	52.2 (10.0)	−0.37 (0.18)	−0.46 (0.18)	0.08 (0.13)	
	6-week	51.0 (11.7)	50.3 (11.2)	56.0 (7.5)	−0.37 (0.19)	−0.40 (0.19)	0.03 (0.13)	
	12-week	51.2 (13.7)	50.7 (14.6)	53.5 (8.5)	−0.22 (0.20)	−0.21 (0.20)	−0.01 (0.14)	
	26-week	52.5 (16.8)	51.0 (14.7)	53.6 (10.7)	−0.03 (0.21)	−0.12 (0.21)	0.08 (0.15)	0.24
BVMT Total Recall T Score	Baseline	44.1 (11.9)	43.1 (11.6)	48.6 (12.2)	−0.33 (0.18)	−0.41 (0.18)	0.08 (0.13)	
	6-week	50.6 (10.7)	49.5 (11.8)	56.3 (10.5)	−0.41 (0.18)	−0.47 (0.19)	0.06 (0.13)	
	12-week	49.9 (13.6)	50.3 (15.5)	55.1 (9.7)	−0.40 (0.19)	−0.34 (0.20)	−0.07 (0.14)	
	26-week	51.2 (17.3)	50.1 (15.4)	52.4 (11.0)	−0.12 (0.21)	−0.13 (0.21)	0.01 (0.15)	0.67
HVLT Delayed Recall T Score	Baseline	48.1 (10.2)	47.4 (11.4)	48.3 (11.0)	−0.02 (0.22)	−0.09 (0.22)	0.08 (0.16)	
	6-week	52.1 (9.1)	49.6 (11.6)	52.6 (8.7)	0.02 (0.22)	−0.26 (0.23)	0.28 (0.16)	
	12-week	52.9 (7.9)	48.9 (10.8)	52.3 (9.8)	0.09 (0.21)	−0.27 (0.21)	0.36 (0.16)	
	26-week	51.8 (8.7)	49.3 (10.9)	53.5 (10.5)	−0.07 (0.21)	−0.33 (0.22)	0.26 (0.15)	0.81
HVLT Total Recall T Score	Baseline	48.9 (9.7)	48.4 (10.3)	48.6 (12.8)	0.03 (0.21)	−0.02 (0.21)	0.05 (0.15)	
	6-week	51.5 (9.9)	51.9 (9.7)	52.7 (9.9)	−0.03 (0.22)	−0.06 (0.22)	0.04 (0.16)	
	12-week	52.3 (7.8)	49.6 (10.4)	52.0 (10.9)	0.03 (0.21)	−0.15 (0.21)	0.18 (0.15)	
	26-week	53.7 (10.4)	52.7 (11.2)	54.6 (12.5)	−0.02 (0.21)	−0.13 (0.22)	0.11 (0.15)	0.85
WMS Logical Memory Scaled Score	Baseline	9.5 (3.0)	9.3 (2.9)	9.3 (3.2)	0.05 (0.22)	0.00 (0.22)	0.05 (0.16)	
	6-week	10.6 (2.7)	10.5 (2.3)	11.1 (2.3)	−0.23 (0.21)	−0.24 (0.21)	0.01 (0.15)	
	12-week	11.1 (2.4)	10.7 (2.7)	11.7 (2.4)	−0.33 (0.21)	−0.38 (0.21)	0.05 (0.15)	
	26-week	11.0 (3.1)	11.2 (2.4)	12.0 (2.8)	−0.45 (0.21)	−0.37 (0.21)	−0.09 (0.15)	0.02
Attention/Concentration								
WAIS Digit Span Scaled Score	Baseline	10.6 (2.9)	10.2 (2.7)	10.7 (2.7)	−0.06 (0.20)	−0.17 (0.20)	0.11 (0.14)	
	6-week	11.2 (3.0)	11.1 (2.8)	10.8 (3.0)	0.11 (0.21)	0.14 (0.21)	−0.03 (0.15)	
	12-week	11.7 (2.9)	10.9 (2.9)	11.7 (3.3)	0.04 (0.21)	−0.10 (0.21)	0.15 (0.15)	
	24-week	11.5 (3.2)	10.7 (3.0)	11.3 (3.0)	0.03 (0.21)	−0.17 (0.21)	0.21 (0.15)	0.50
Color Trails T score Trial 1	Baseline	50.7 (9.1)	49.3 (9.0)	53.6 (5.5)	−0.29 (0.18)	−0.42 (0.18)	0.13 (0.12)	
	6-week	51.8 (7.7)	51.3 (8.7)	55.7 (4.5)	−0.40 (0.18)	−0.43 (0.18)	0.03 (0.13)	
	12-week	54.2 (11.0)	53.8 (11.7)	54.8 (5.5)	−0.15 (0.19)	−0.11 (0.19)	−0.04 (0.14)	
	26-week	57.8 (14.33)	55.7 (12.5)	56.4 (4.3)	0.16 (0.21)	0.03 (0.21)	0.13 (0.15)	0.05
Executive Function								
Color Trails T score Trial 2	Baseline	53.0 (10.5)	51.8 (10.9)	55.1 (7.7)	−0.18 (0.18)	−0.29 (0.18)	0.11 (0.13)	
	6-week	54.9 (8.7)	53.2 (10.9)	56.5 (6.5)	−0.20 (0.18)	−0.35 (0.18)	0.15 (0.13)	
	12-week	56.2 (11.3)	56.3 (13.8)	58.1 (6.0)	−0.21 (0.19)	−0.23 (0.19)	0.02 (0.14)	
	24-week	58.9 (14.8)	57.2 (15.0)	59.2 (6.4)	−0.06 (0.21)	−0.20 (0.21)	0.14 (0.15)	0.60
Stroop Color Task Score	Baseline	111.0 (6.9)	111.8 (2.5)	111.5 (1.6)	−0.15 (0.31)	0.10 (0.31)	−0.25 (0.22)	
	6-week	111.8 (1.2)	111.9 (0.2)	111.9 (0.6)	−0.02 (0.25)	−0.01 (0.25)	−0.01 (0.18)	
	12-week	111.5 (2.7)	112.0 (0.2)	112.0 (0.2)	−0.09 (0.2)	0.00 (0.21)	−0.09 (0.15)	
	26-week	111.2 (5.4)	111.9 (0.3)	111.9 (0.4)	−0.18 (0.21)	0.00 (0.21)	−0.17 (0.15)	0.48
Stroop Color-Word Score	Baseline	93.1 (20.4)	93.0 (20.1)	99.4 (13.7)	−0.34 (0.21)	−0.34 (0.21)	0.01 (0.15)	
	6-week	98.3 (18.6)	93.6 (20.6)	102.4 (12.2)	−0.27 (0.22)	−0.53 (0.22)	0.25 (0.16)	
	12-week	99.4 (18.9)	97.2 (16.9)	104.0 (12.3)	−0.24 (0.21)	−0.39 (0.21)	0.15 (0.15)	
	26-week	99.1 (19.4)	97.5 (18.7)	101.0 (17.5)	−0.14 (0.21)	−0.22 (0.21)	0.08 (0.15)	0.36

(*continued*)

TABLE 3. (CONTINUED)

		MBSR	*BCES*	*Control*	*MBSR vs. Control*	*BCES vs. Control*	*MBSR vs. BCES*	
Memory	*Time*	*Mean (SD)*[a]	*Mean (SD)*[a]	*Mean (SD)*[a]	*d (se)*[b]	*d (se)*[b]	*d (se)*[b]	p-Value*
Verbal Fluency COWA Total	Baseline	38.5 (12.3)	35.5 (11.5)	41.2 (12.1)	−0.23 (0.21)	−0.49 (0.21)	0.26 (0.15)	
	6-week	42.0 (11.1)	37.1 (10.2)	39.5 (10.4)	0.11 (0.21)	−0.29 (0.21)	0.40 (0.15)	
	12-week	43.6 (11.2)	39.1 (11.2)	42.6 (12.4)	0.04 (0.21)	−0.29 (0.21)	0.33 (0.15)	
	26-week	44.3 (11.8)	39.7 (11.7)	42.5 (11.1)	0.10 (0.21)	−0.23 (0.21)	0.32 (0.15)	0.13

[a]Observed means and standard deviations.
[b]Difference of least-squares means and standard error (se) from general linear mixed model with scaled (z-score) outcome and group, time, and group × time interaction as predictors; estimates at each time point were computed from separate models utilizing data up to that time point.
*p-Value for the order restricted (MBSR > BCES > UC) time × group interaction for improvement.
PROMIS, Patient-Reported Outcomes Measurement Information System.

time (Table 5); however, the reduction in fatigue was the largest and statistically significant (p = 0.003) for the MBSR(BC) group with a 26-week pairwise effect size of 0.45 and 0.65 compared with the BCES and UC groups, respectively. The MBSR(BC) group showed greater reductions in depression compared with BCES and UC, with no significant between-group differences; however, the MBSR(BC) group had a nominally larger effect size of 0.50 and 0.53 compared with BCES effect size of 0.35 or UC 0.17. Similarly, both groups, MBSR(BC) and BCES reported reductions in pain interference with no significant differences occurring; however, the MBSR(BC) effect size was 0.61 compared with the BCES effect size of 0.42 at 26 weeks.

Assessment of within-group effect sizes

Given similar between-group improvements, within-group effect sizes were calculated to assess the magnitude of improvement. For subjective measures of cognitive performance, all groups improved on all four outcomes and within-group effect sizes were ≥0.50, with a reduction in perceived cognitive ability and quality of life. As previously observed, the reduction in fatigue at 26 weeks was greatest in the MBSR(BC) group (effect size = 0.81) (Fig. 2). For all 10 measures of objective cognitive performance, all groups showed improvement (positive effect size) at 26 weeks (Fig. 3). The general pattern of means was examined to determine if it occurred randomly or in the hypothesized direction. For all groups, the effect sizes were found to *occur in order of the hypothesized direction* or pattern by *first* MBSR(BC) > BCES > UC for 10 of the 18 outcomes. The likelihood of this exact order in 10 or more of the subscales is 0.02%.

Assessment of effect modification

A subgroup analysis of BCS enrolled within 1 year of CT completion showed that within-group effect sizes for perceived cognitive abilities, perceived cognitive impairments, and QOL were highest for the MBSR(BC) group (effect size 0.72–1.19), lower for the BCES group (effect size 0.58–0.90), and the lowest for the UC group (effect size 0.01–0.38) (Fig. 4). The within-group effect size for objective cognitive measures did not show beneficial evidence in the MBSR(BC) group (Fig. 5). Beneficial evidence was absent for MBSR(BC) on subjective and objective cognitive performance after 1-year of chemotherapy completion (Figs. 6 and 7). No adverse events were reported as a result of participation in either the MBSR(BC) or BCES programs.

Discussion

Results of this large RCT showed that all three groups [MBSR(BC), BCES, UC] demonstrated meaningful improvements in both subjective and objective measures of cognitive performance over 26 weeks. Although minimal between-group differences occurred in cognitive performance over time, within-group effect sizes frequently exceeded 0.50 (i.e., "medium" effect size or larger) for all groups. In addition, effect sizes occurred in the hypothesized direction (i.e., MBSR[BC] largest, BCES intermediate, UC smallest) in 10 of 18 outcomes. Since the pattern of effect sizes frequently occurred in the hypothesized order, and at an unlikely random rate (0.02%), this suggests that

Table 4. Subjective Cognition: Means and Standard Deviations (SD) by Treatment Group and Timepoint; Pairwise Effect Sizes and *P*-Values

		MBSR	*BCES*	*Control*	*MBSR vs. Control*	*BCES vs. Control*	*MBSR vs. BCES*	
Measure	*Time*	*Mean (SD)*[a]	*Mean (SD)*[a]	*Mean (SD)*[a]	*d (se)*[b]	*d (se)*[b]	*d (se)*[b]	p-Value*
FACT Comments from Others	Baseline	3.4 (0.8)	3.3 (0.7)	3.5 (0.7)	–0.26 (0.23)	–0.29 (0.23)	0.03 (0.17)	
	6-week	3.6 (0.6)	3.5 (0.7)	3.3 (0.7)	0.30 (0.24)	0.13 (0.24)	0.17 (0.17)	
	12-week	3.7 (0.5)	3.6 (0.6)	3.5 (0.6)	0.24 (0.22)	0.07 (0.22)	0.17 (0.16)	
	26-week	3.6 (0.6)	3.5 (0.7)	3.6 (0.6)	0.19 (0.22)	0.0 (0.22)	0.19 (0.16)	0.12
FACT Impairments on Quality of Life	Baseline	2.4 (1.1)	2.1 (1.2)	2.4 (0.9)	–0.02 (0.21)	–0.27 (0.21)	0.26 (0.15)	
	6-week	2.9 (1.0)	2.4 (1.1)	2.6 (1.0)	0.28 (0.22)	–0.22 (0.22)	0.50 (0.16)	
	12-week	3.0 (1.0)	2.7 (1.1)	2.8 (1.0)	0.25 (0.21)	–0.12 (0.21)	0.37 (0.15)	
	26-week	3.1 (1.0)	2.8 (1.1)	3.0 (1.0)	0.24 (0.21)	–0.04 (0.21)	0.28 (0.15)	0.61
FACT Perceived Cognitive Abilities	Baseline	2.2 (0.8)	2.1 (0.8)	2.1 (0.8)	0.13 (0.19)	–0.01 (0.19)	0.14 (0.14)	
	6-week	2.6 (0.8)	2.3 (0.8)	2.3 (0.9)	0.45 (0.21)	0.11 (0.21)	0.34 (0.15)	
	12-week	2.6 (0.8)	2.4 (0.9)	2.3 (0.9)	0.32 (0.21)	0.09 (0.21)	0.23 (0.15)	
	26-week	2.7 (0.9)	2.5 (0.8)	2.5 (1.1)	0.28 (0.21)	0.10 (0.21)	0.18 (0.15)	0.96
FACT Perceived Cognitive Impairments	Baseline	2.1 (0.9)	2.1 (0.9)	2.3 (0.8)	–0.22 (0.22)	–0.23 (0.22)	0.01 (0.15)	
	6-week	2.6 (0.7)	2.2 (0.9)	2.3 (0.7)	0.24 (0.22)	–0.17 (0.22)	0.41 (0.16)	
	12-week	2.6 (0.8)	2.4 (0.9)	2.5 (0.8)	0.22 (0.21)	–0.11 (0.21)	0.33 (0.15)	
	26-week	2.8 (0.7)	2.6 (0.8)	2.7 (0.7)	0.23 (0.21)	–0.01 (0.21)	0.24 (0.15)	0.12

[a]Observed means and standard deviations.

[b]Difference of least-squares means and standard error from general linear mixed model with scaled (z-score) outcome and group, time, and group × time interaction as predictors; estimates at each time point were computed from separate models utilizing data up to that time point..

**p*-Value for the order restricted (MBSR > BCES > UC) time × group interaction for improvement.

FACT, Functional Assessment of Cancer Therapy.

Table 5. Symptom Response Means and Standard Deviations (SD) by Treatment Group and Time Point; Pairwise Effect Sizes and *P*-Values

		MBSR	*BCES*	*Control*	*MBSR vs. Control*	*BCES vs. Control*	*MBSR vs. BCES*	
Measure	*Time*	*Mean (SD)*[a]	*Mean (SD)*[a]	*Mean (SD)*[a]	*d (se)*[b]	*d (se)*[b]	*d (se)*[b]	p-Value*
PROMIS Anxiety	Baseline	4.5 (3.6)	4.7 (3.7)	4.9 (3.8)	−0.13 (0.22)	−0.07 (0.22)	−0.06 (0.16)	
	6-week	4.0 (3.3)	4.8 (3.6)	4.5 (2.9)	−0.22 (0.22)	0.05 (0.23)	−0.27 (0.16)	
	12-week	3.6 (3.1)	4.4 (3.5)	3.5 (2.8)	−0.08 (0.22)	0.22 (0.22)	−0.03 (0.16)	
	26-week	3.3 (3.1)	3.8 (3.5)	3.5 (3.5)	−0.16 (0.21)	0.06 (0.21)	−0.22 (0.15)	0.86
PROMIS Depression	Baseline	2.8 (3.1)	3.3 (3.4)	3.6 (4.1)	−0.26 (0.22)	−0.08 (0.22)	−0.18 (0.16)	
	6-week	2.4 (3.0)	2.9 (3.1)	3.7 (3.7)	−0.50 (0.23)	−0.29 (0.23)	−0.21 (0.16)	
	12-week	1.9 (2.5)	2.8 (2.9)	3.5 (4.1)	−0.53 (0.22)	−0.22 (0.22)	−0.31 (0.16)	
	26-week	1.7 (2.5)	2.7 (3.1)	2.6 (3.2)	−0.53 (0.22)	−0.17 (0.22)	−0.35 (0.16)	0.67
PROMIS Fatigue	Baseline	8.4 (4.2)	8.3 (4.3)	8.6 (3.8)	−0.05 (0.22)	−0.08 (0.21)	0.02 (0.15)	
	6-week	6.1 (4.2)	8.6 (4.3)	8.0 (3.5)	−0.45 (0.22)	0.15 (0.22)	−0.60 (0.16)	
	12-week	6.8 (4.3)	7.9 (4.0)	8.2 (4.0)	−0.45 (0.21)	−0.01 (0.22)	−0.44 (0.16)	
	26-week	5.2 (3.6)	7.0 (4.4)	7.6 (4.0)	−0.65 (0.21)	−0.19 (0.21)	−0.45 (0.15)	0.003
Pain Interference	Baseline	10.9 (7.8)	12.3 (8.9)	11.3 (8.8)	−0.26 (0.22)	0.11 (0.27)	−0.17 (0.17)	
	6-week	9.2 (7.9)	11.6 (7.4)	10.5 (9.2)	−0.06 (0.27)	0.09 (0.27)	−0.28 (0.17)	
	12-week	9.8 (8.3)	12.0 (8.9)	9.8 (9.2)	−0.18 (0.27)	0.10 (0.27)	−0.24 (0.17)	
	26-week	9.2 (7.8)	10.7 (8.5)	14.5 (9.5)	−0.61 (0.26)	−0.42 (0.26)	−0.20 (0.16)	0.07

[a]Observed means and standard deviation.

[b]Difference of least-squares means and standard error (se) from general linear mixed model with scaled (z-score) outcome and group, time, and group × time interaction as predictors; estimates at each time point were computed from separate models utilizing data up to that time point.

**p*-Value for the order restricted (MBSR > BCES > UC) time × group interaction for improvement.

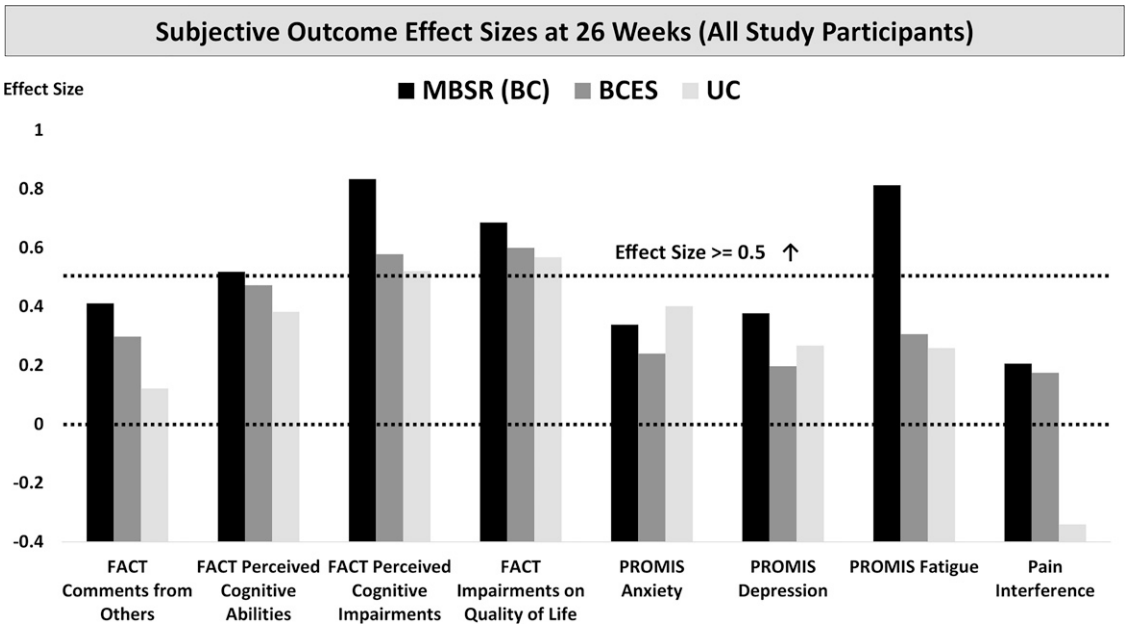

FIG. 2. Cohen's *d* within-group effect sizes for the subjective measures of cognitive performance. These effect sizes indicate improvement from baseline to the 26-week time point for Mindfulness-Based Stress Reduction (MBSR[BC]), Breast Cancer Education Support (BCES), and Usual Care (UC).

effect size differences favoring MBSR(BC) may have been too small to be detected statistically.

Due to the effects of randomization, this trial corrected for selection bias (BCS did not self-select into each group). Performance bias was considered when BCS randomly assigned to conditions were asked about prior use of techniques similar to MBSR (meditation, yoga, and guided imagery) at baseline. All three groups were similar in their experience. The ranges of experience (and *p*-value for the chi-square comparison between groups) were the following: meditation 11%–23% ($p = 0.26$), yoga 6%–11% ($p = 0.35$), and guided imagery 6%–9% ($p = 0.92$). Randomization minimized differences in characteristics between participants, thus correcting for "detection bias" showing that participant characteristics influence how information is collected. "Attrition bias" was corrected by including all follow-up data in the analyses, even if they did not complete all three time points. These analyses included 89% of MBSR(BC) participants; 88% of BCES participants; and 87% of UC participants, indicating no systematically different attrition between groups.

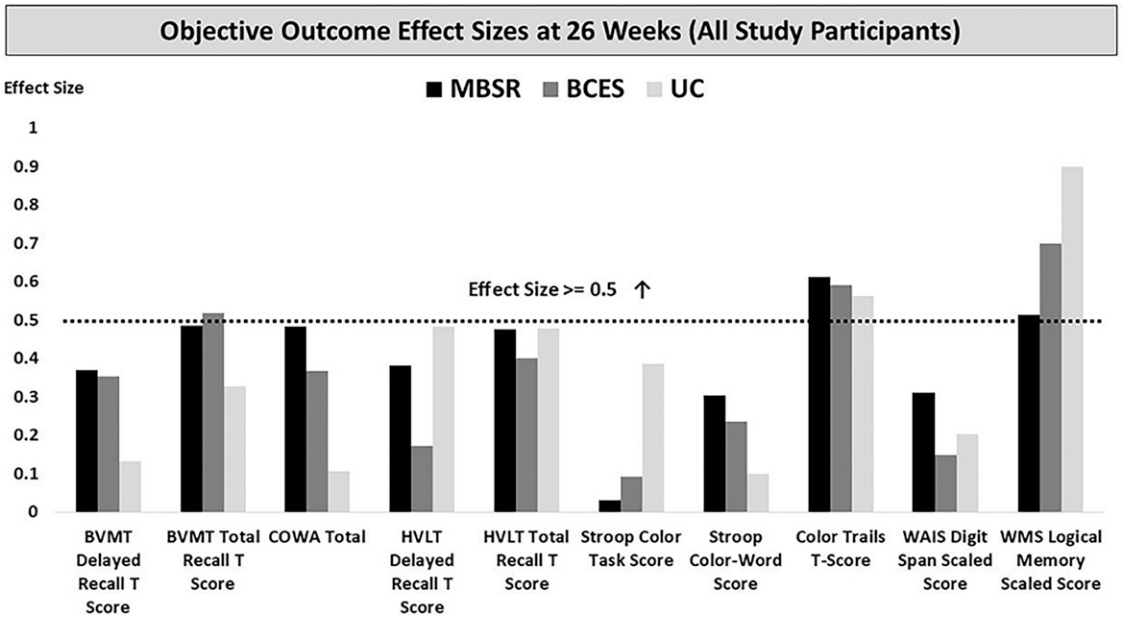

FIG. 3. Cohen's *d* within-group effect sizes for objective outcomes. These effect sizes indicate improvement from baseline to the 26-week time point for Mindfulness-Based Stress Reduction (MBSR[BC]), Breast Cancer Education Support (BCES), and Usual Care (UC).

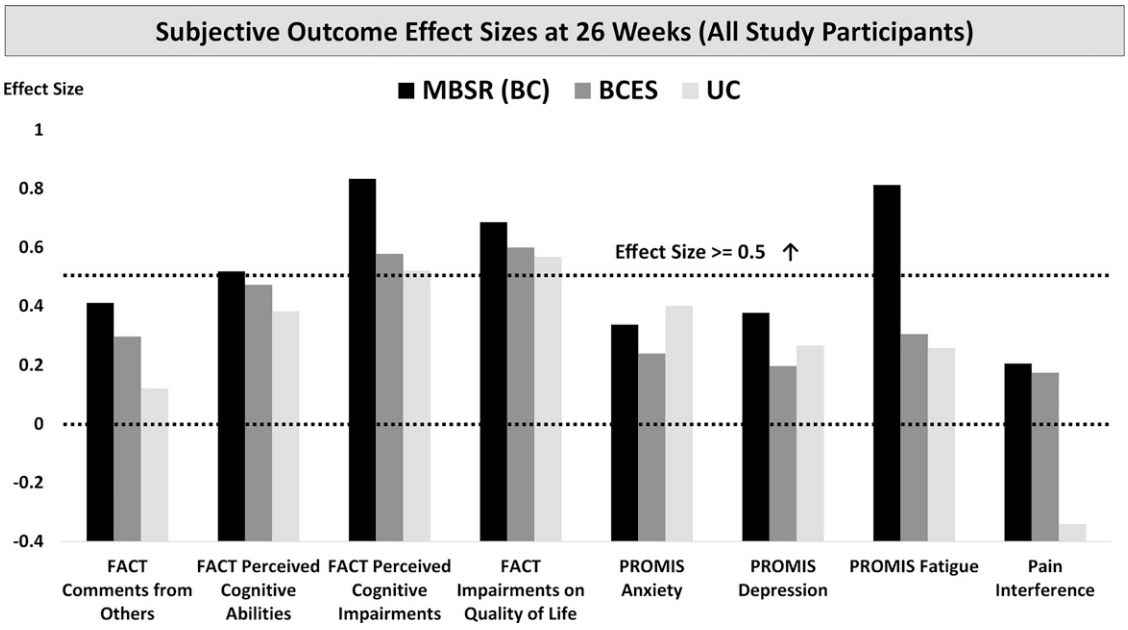

FIG. 4. Cohen's *d* within-group effect sizes for subjective outcomes in patients who have been out of cancer treatment for one year or less. These effect sizes indicate improvement from baseline to the 26-week time point for Mindfulness-Based Stress Reduction (MBSR[BC]), Breast Cancer Education Support (BCES), and Usual Care (UC).

Compared with this study, there continues to be limited research on objective cognitive functioning and MBSR and BCS. A small RCT with an attention control group among BCS and colorectal patients found significant improvement in objective attention and sustained executive functioning in the MBSR group.[37] Our prior RCT comparing MBSR(BC) to UC (only) showed reductions in psychological and physical symptoms, QOL[38,39]; symptom clusters[40,41]; and greater subjective cognitive performance,[42] compared with improvement in outcomes in both the MBSR(BC) and BCES groups in this study.

Therefore, upon closely examining the results of this study, three plausible explanations may be presented. First, this trial showed the benefits of a well-designed "attention control" BCES education program. Patients in both the MBSR(BC) and the BCES program improved at 26 weeks in

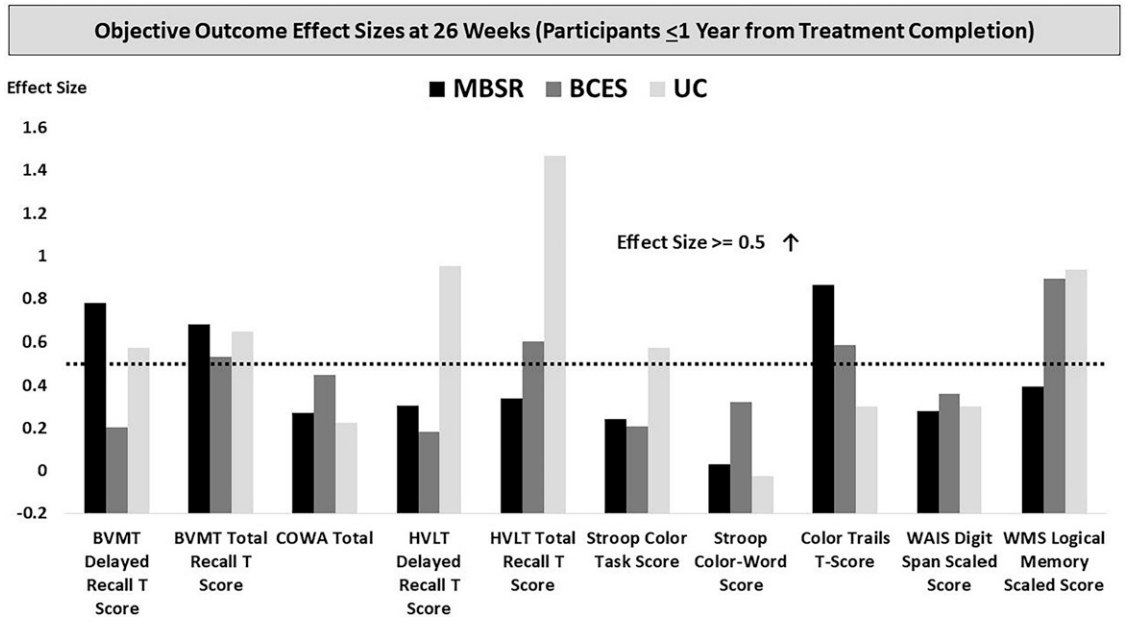

FIG. 5. Cohen's *d* within-group effect sizes for objective outcomes in patients who have been out of cancer treatment for one year or less. These effect sizes indicate improvement from baseline to the 26-week time point for Mindfulness-Based Stress Reduction (MBSR[BC]), Breast Cancer Education Support (BCES), and Usual Care (UC).

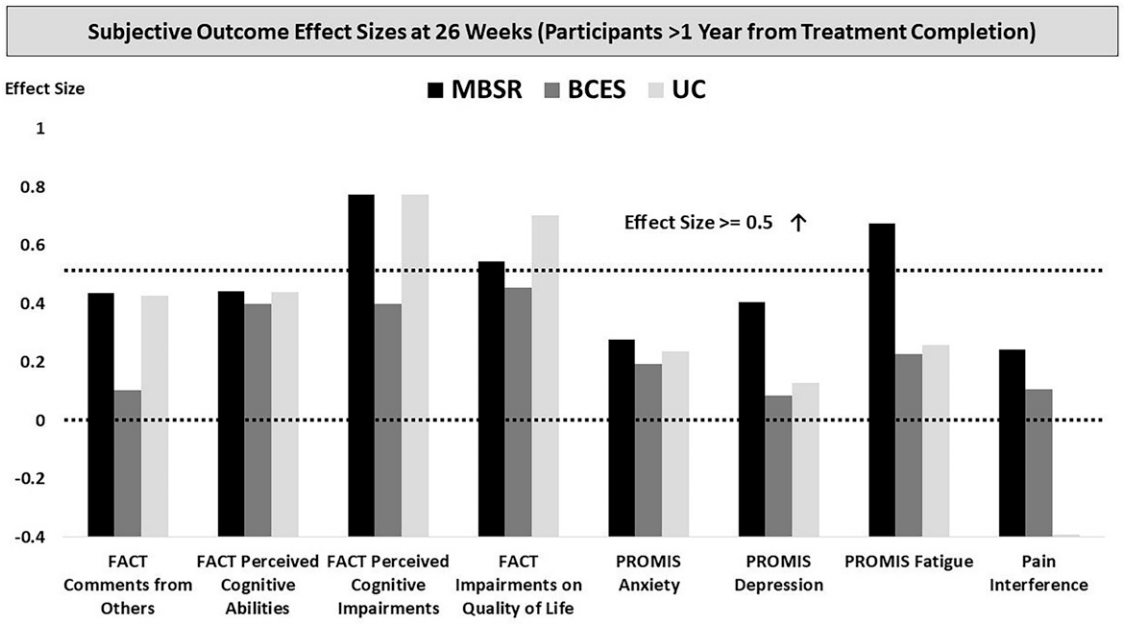

FIG. 6. Cohen's *d* within-group effect sizes for subjective outcomes in patients who have been out of cancer treatment for more than 1 year. These effect sizes indicate improvement from baseline to the 26-week time point for Mindfulness-Based Stress Reduction (MBSR[BC]), Breast Cancer Education Support (BCES), and Usual Care (UC).

their hypothesized directions for *subjective cognitive* and *symptom improvements*; however, this was not evident in *objective cognitive performance.*

A second explanation is related to the primary inclusion criterion of evidence of cognitive impairment ("chemo brain") and the long follow-up at 6 months. Research demonstrates that cognitive functioning (brain imaging abnormalities) may improve after completion of chemotherapy[65] suggesting potentially reversible effects among all three conditions due to the natural history of cognitive functioning after chemotherapy.

Third, BCS enrolled in clinical trials frequently differ from nonparticipants in health-related ways, with a higher self-efficacy,[66] fewer comorbidities, less medication use,[67,68] and simply benefiting from participation.[69] In our trial of 1362 eligible approached patients, 18.6% verbally agreed to participate (Fig. 1), and most exercised at 2–4 days per week (Table 1). Enrolled BCS may have been health motivated to

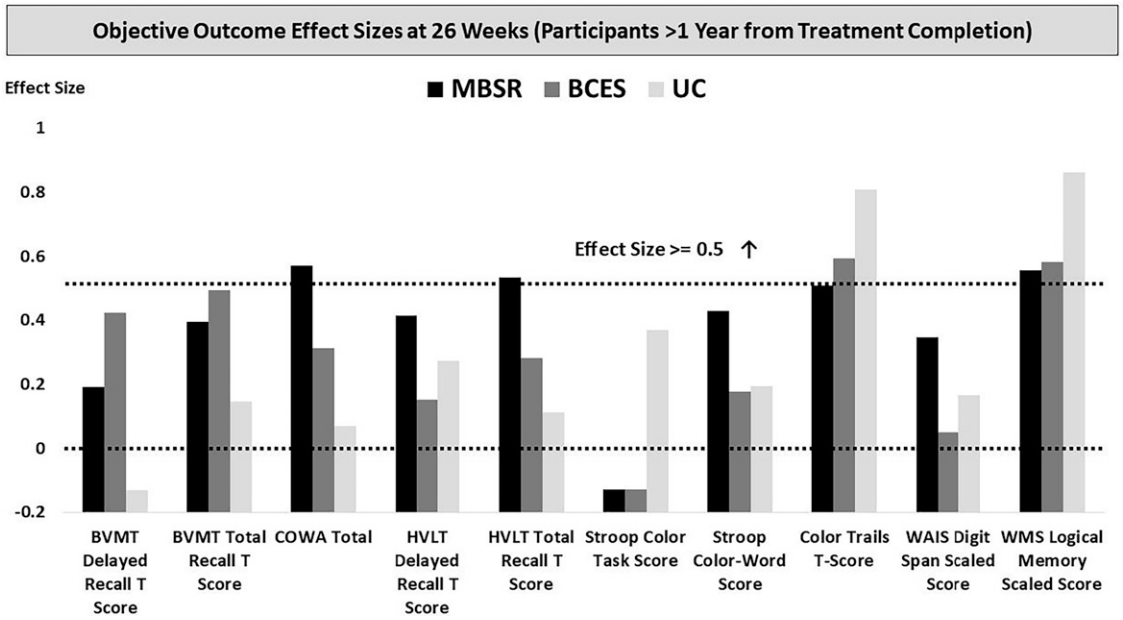

FIG. 7. Cohen's *d* within-group effect sizes for objective outcomes in patients who have been out of cancer treatment for more than 1 year. These effect sizes indicate improvement from baseline to the 26-week time point for Mindfulness-Based Stress Reduction (MBSR[BC]), Breast Cancer Education Support (BCES), and Usual Care (UC).

Table 6. Consort Checklist—American Medical Association 2010

Section	*Item number*	*Checklist item*	*Reported on*
Title and Abstract	1a	Identification of Randomized Trial in the title	Page 1
	1b	Structured summary of trial design, methods, results, and conclusions	Page 11
Introduction, Background, and Objectives	2a	Specific Background and Explanation of 2b	Pages 13–15
	2b	Specific Objective	Page 15
Methods	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Pages 15–16
Trial Design	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Pages 15–16, 23
Participants	4a	Eligibility criteria for participants Settings and locations where the data were collected	Page 15
	4b		
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were administered	Pages 16–17
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed.	Page 15
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample Size	7a	How sample size was determined When applicable, explanation of any interim analyses and stopping guidelines	Page 16
	7b		
Randomization	8a	Method used to generate the random allocation sequence	Pages 15–16
Sequence Generation	8b	Type of randomization; details of any restriction (such as blocking and block size)	Pages 15–16
Allocation Concealment Mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Pages 15–16
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions?	Pages 15–16
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	Pages 16–17
	11b	If relevant, description of the similarity of interventions	
Statistical Methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Pages 18–19
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome.	Page 19
Participant Flow	13b	For each group, losses and exclusions after randomization, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up.	Page 15
	14b	Why the trial ended or was stopped	
Baseline Data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Number Analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by originally assigned groups	Figure 1
Outcomes and Estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Pages 20–21
Ancillary Analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	Pages 20–21
Harms	19	All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms)	Page 22
Comment Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Page 23
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	Pages 19–21
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Pages 22–23
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PROMIS, Patient-Reported Outcomes Measurement Information System.

participate in health-promoting activities independent of random assignment.

Clinical implications of findings

Currently, no solution exists for the pervasive adverse side effects of chemotherapy resulting in loss of memory and executive functioning. Although the MBSR(BC) program did not result in significant cognitive beneficial between-group differences, it did result in long-term reductions in fatigue, a clinically relevant outcome confirming previous work among BC populations.[38] Importantly, since fatigue severity is strongly associated with cognitive performance among BCS,[70] future work may explore fatigue's role in cognition, specifically due to the influence of MBSR(BC) on fatigue.

Strengths and limitations

To our knowledge, this is the largest RCT evaluating the effects of an MBSR(BC) program on objective and subjective cognitive performance over 26 weeks after chemotherapy. As identified, our sample was generally well educated with almost half having a college education, and seemingly health conscious after diagnosis and treatment, as indicated by frequent routine engagement in exercise—this limits the generalizability of our results. Recruitment challenges also occurred when BCS preferred enrollment (random assignment) in the BCES or MBSR(BC) program rather than the UC regimen, which required a 26-week wait time before being offered the MBSR(BC) program. To overcome this barrier to recruitment and retention, random assignment to the UC group was capped after 30 subjects were enrolled, thereby reducing statistical power for outcome comparisons with this group. Another limitation may have been the inclusion of a large percentage of BCS who received radiation in conjunction with chemotherapy (i.e., rather than isolated chemotherapy). Although "chemo brain" affects BCS years after treatment ends,[4–10] evidence indicates that BCS treated with chemotherapy and radiation therapy report higher cognitive impairment.[11] This dual treatment may be a marker for more severe disease and precludes direct assessment of the effect of MBSR(BC) following chemotherapy alone. Future work should consider examining radiation treatment as a moderator on the effects of MBSR following chemotherapy.

Conclusions

Although no significant differences in cognitive performance were observed *overall at 26 weeks* between MBSR(BC), BCES, and UC, all three groups improved substantially over time, along with significant reductions in fatigue reported for the MBSR(BC) group. Results suggest that cognitive performance improves over time for BCS treated with chemotherapy (natural history), and selected BCS enrolled in RCTs may be particularly motivated to improve their health status after CT. Although beyond the scope of this article, future consideration will be given to examining potential mediators of MBSR (stress, rumination, and mindfulness) that may influence the outcome of cognitive performance among BCS.

Authors' Contributions

C.L. initiated and conceptualized the research objectives and questions, designed the programs, and applied for funding as the principal investigator in the study. K.K., R.R., H.M., and G.H. were responsible for the methodology related to data analysis. M.M. and E.B. contributed to the delivery of the mindfulness intervention, whereas C.R. contributed to the design and delivery of the BCS educational program. K.D. was the site principal investigator for Moffitt Cancer Center. T.F. was the site coordinator for Sarasota Memorial Health Care System, and J.L. was the site principal investigator for Sarasota Memorial Health Care System. C.L. was the creator of the protocol article with contributions from R.R. and J.P. All authors contributed to the implementation of the protocol and review of the final version. All authors revised the article and approved the final version to be published. The CONSORT checklist was followed during the development of this manuscript (Table 6).

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No competing financial interests exist.

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