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Cognitive rehabilitation group intervention for breast cancer survivors: results of a randomized clinical trial

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Abstract

***Purpose*: We conducted a randomized clinical trial evaluating the efficacy of a cognitive rehabilitation (CR) intervention compared with a wait list (WL) control condition on cognitive complaints, neuropsychological and brain functioning in breast cancer survivors (BCS).**

***Methods*: The small group intervention of five sessions included psychoeducation and cognitive exercises.**

***Eligibility*: Disease-free BCS with cognitive complaints, diagnosed with stage I, II or III breast cancer, completed primary treatment 18 months to 5 years earlier. Neurocognitive test data and cognitive complaints on the Patient's Assessment of Own Functioning Inventory (PAOFI) were assessed at baseline (T1), immediately post-intervention (T2), and 2 months later (T3). A subgroup of participants underwent resting state quantitative electroencephalography (qEEG) at all three assessment time points.**

***Results*: Forty-eight participants [mean age (SD) 53.8 (8.2)] completed T1 assessments, and 29 participants had analyzable qEEG data. The CR group improved significantly over time compared with the WL group on PAOFI total and memory scores (both $p = .01$) and on Rey Auditory Verbal Learning Test (RAVLT) total (trials I–V) ($p = .02$) and RAVLT delayed recall ($p = .007$) scores. On qEEG, the CR group showed a significant decrease in delta 'slow wave' power ($p = .02$) and an increase in the frontal distribution of alpha power ($p = .04$) from T1 to T2.**

***Conclusions*: BCS in the CR group showed immediate and sustained improvements in self-reported cognitive complaints and memory functioning on neurocognitive testing. Results of the qEEG substudy provide some support for neurophysiological changes underlying the intervention.**

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Introduction

Many patients with breast cancer report cognitive difficulties during and after cancer treatments [1,2], and up to 35% complain of persistent and sometimes disabling cognitive difficulties [3–7]. Although the causal mechanisms of post-treatment cognitive difficulties have not been fully elucidated, a sizeable number of breast cancer survivors (BCS) have persistent difficulties with need for rehabilitation strategies.

We previously described a 5-week cognitive rehabilitation (CR) intervention program for BCS and tested its feasibility in a single arm study in 27 BCS [8], including preliminary evaluation of quantitative electroencephalography (qEEG) as a physiological biomarker of intervention effects. The pilot study findings supported possible immediate and sustained improvements in cognitive complaints and neurocognitive function, identifying specific outcome measures with effect size (ES) estimates for use in a phase II randomized controlled trial (RCT) whose results we report here.

Methods

Study design, eligibility, and participant recruitment

This was a two-group RCT with participants assigned to CR or wait list (WL) control. Eligibility were female; age 21 to 75 years; history of stage 0, I, II, III breast cancer with treatments completed between 18 months and 5 years earlier; current endocrine therapy allowed; able to read and speak English; self-reported cognitive difficulties interfering with everyday activities; able to provide written informed consent. Exclusion criteria were current uncontrolled depression using a standardized screening measure; another current psychiatric disorder; concurrent psychoactive medications such as sedatives, hypnotics, opiates taken chronically; central nervous system

disorders or past cranial radiation or intrathecal chemotherapy; history of head trauma, seizure disorder, learning disability, or regular and heavy use of illicit substances or alcohol. The study and its procedures were approved by the University of California, Los Angeles Institutional Review Board, and the trial was registered at Clinical Trials.gov (NCT01540955). All participants provided written informed consent.

Participants were recruited through multiple mechanisms, including clinic flyers, internet posting by the Army of Women, community presentations, and direct referral by oncology clinicians. Potentially interested women were screened for eligibility by telephone that included specific questions designed to assess severity of cognitive complaints. Affirmative responses were required on three questions prior to formal cognitive screening: 'Do you think or feel that your memory or mental ability has gotten worse since you completed your breast cancer treatment?', 'Do you think that your mind isn't as sharp now as it was before your breast cancer treatments?' and 'Do you feel like these problems have made it harder to function on your job or take care of things around the home?' We then administered the memory scale of the Patients Assessment of Own Functioning (PAOFI) [9], and at least 1 of the 10 items had to be endorsed as moderately severe to be included in the study. Depressive symptoms were also screened with a standardized measure. [10]. Only after successful screening were women invited to join the study.

Study procedures and intervention program

Eligible women were invited to an in-person baseline assessment (T1) prior to randomization at which time written informed consent was obtained. Baseline visits were scheduled when a sufficient number of participants were identified to form a study cohort whose members would be randomly assigned to the CR group or WL group who would receive the CR at a delayed time point. Randomization was carried out in blocks of 3, with a 2:1 ratio of assignment to CR versus WL, to facilitate study enrollment and retention, given the high level of symptoms in this population. Random assignments were placed in consecutively ordered sealed envelopes that were opened after baseline testing. Subsequent study assessments occurred post-intervention (T2) (within a week of completing the CR or at the same time interval for those in the WL group in the cohort) and 2 months following the intervention (T3) for the CR and WL groups in the cohort. At each time point, assessments included neurocognitive testing and self-report questionnaires about mood and cognition. All participants were approached to participate in an EEG substudy described in the succeeding texts.

The 5-week, 2-h per week, manualized group intervention targeted attention (weeks 1–2), executive (week 3) and memory (week 4) functions and a review (week 5). Intervention components included education, technique instruction, in-class and homework exercises and goal setting [11–15]. Each participant received a training manual/workbook and could complete the exercises at home in the case of an absence. The intervention was delivered over five consecutive weeks by one of three separate clinicians, who were trained in the intervention content and monitored for fidelity of delivery. The intervention, described in detail in a prior publication [8], has theoretical underpinnings in cognitive training and CR [13,15].

Demographic, clinical and patient-reported outcomes

Participants completed a self-report questionnaire at (T1) that provided information on age, marital status, education, income and employment. Information on current medications, including endocrine therapy for breast cancer, were also obtained. Medical chart abstraction was conducted at the end of the study to obtain information on breast cancer stage and initial treatments to describe the participant characteristics. At all assessment time points, patients also completed the PAOFI [9], a 33-item scale assessing presence and frequency of cognitive difficulties, yielding a total score (range 0–33) and scale scores in four domains—memory, language and communication, motor and sensory-perceptual function, and higher level cognition. The PAOFI was used in our pilot study [8] and other studies with BCS [16,17] and found to be useful in identifying domain-specific cognitive complaints. Higher scores indicate more severe complaints. The Beck Depression Inventory, 2nd Edition [18] (BDI-II) was used to assess depressive symptoms. Standard cutoff scores indicate minimal (0–9), mild (10–18), moderate (19–29), or severe (30–63) depression.

Neurocognitive assessment

Cognitive testing was conducted by a trained technician who was masked to the intervention assignment. The assessment battery included the Brief Visual Memory Test-Revised[19], the Rey Auditory Verbal Learning Test (RAVLT) [20], verbal fluency tests [21], the Paced Auditory Serial Addition Test, [22], and Trail Making Tests [23]. Alternate forms, when available, were used at the different time points. The computerized CNS Vital Signs [24] was used to assess aspects of attention and information processing speed. This battery retained the assessments used in our pilot study [8]; however, we used the RAVLT as a replacement for the Hopkins Verbal Learning Test [25] as we were concerned about a potential ceiling effect on the latter. Raw scores on all measures were converted to standardized scores for outcome analyses with higher scores representing better performance. Premorbid IQ was estimated using the Wechsler Test of Adult Reading (WTAR) [26].

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Quantitative EEG (qEEG) procedures

We recorded awake, resting state EEGs at T1, T2, and T3, from 35 scalp electrodes using methods identical to those reported previously [8,27]. Absolute power (μV^2) and relative power (percentage of total power) were calculated for each channel in: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–20 Hz). All participants were approached to participate in this substudy, but some were not included either because of difficulties in scheduling or absence of a technician to perform the study.

Data analysis

Sample size and power for the study were based on our earlier pilot study in which we observed statistically significant improvement in the PAOFI total and memory subscale cognitive complaints, with ES of .479 and .517 respectively from pre-intervention to immediate post-intervention assessments. Several neurocognitive tests demonstrated improvement from pre-intervention to immediate post-intervention assessments in the pilot study, including the Symbol Digit correct, the Stroop complex reaction time, and the Trails A time with ES of 0.429, 0.607 and 0.324 respectively. However, the reliable change index analyses indicated that reliable improvement was most often seen on measures of verbal learning and memory (Hopkins Verbal Learning Test-Revised) and processing speed (Symbol Digit) at the immediate post-intervention time point. The sample size for the current study was based on the PAOFI total score as the primary endpoint. The PAOFI memory scale was examined as a secondary endpoint. Power calculations for general linear models indicated that group sizes of 34 and 17 in a 2:1 randomization would provide 80% power to detect a standard ES of 0.5 for difference in change over time, assuming within-participant correlation of 0.8, with alpha of 0.05. To account for potential attrition of 10%, we targeted a total enrollment of 56 participants. The neurocognitive test results were secondary endpoints, and we focused on the RAVLT as the neurocognitive test of interest.

Bivariate analyses (*t*-tests for continuous variables, chi-squared and Fisher's exact tests for categorical variables) were used to compare baseline demographic, medical, and psychosocial variables, as well as PAOFI and neuropsychological test scores, between the CR and WL groups. Mixed models were used to test for longitudinal differences between the CR and WL groups across all three time points for the PAOFI total score controlling for the baseline values, as well as for other baseline covariates (age, employment, BDI-II, years since diagnosis, current endocrine therapy, and prior chemotherapy and radiation). All patient data were included using an intention-to-treat principle. Secondary exploratory endpoints (PAOFI memory score and the RAVLT), were examined using the same analytic approach.

The qEEG analyses compared CR and WL conditions on changes in global absolute and relative power measures (means across all recording channels) for each frequency band. Based upon prior work [8], we also examined changes in the anterior–posterior (AP) gradient of absolute alpha power. AP gradient = ((anterior − posterior)/(anterior + posterior)), where 'anterior' is the mean power across electrodes Fp1, F3, F7, Fp2, F4, F8, Fz, Cz and 'posterior' is the mean power across electrodes P3, O1 P4, O2 and Pz [28]. After establishing that there were no significant qEEG differences at baseline, we used independent *t*-tests to compare the CR and WL groups on qEEG changes from T1 to T2. qEEG changes that differed significantly between groups at T2 ($p < .05$, uncorrected) were then examined in separate linear regression models as predictors of change in PAOFI total scores at T2 and T3, controlling for age and estimated IQ. qEEG changes at T2 that showed a significant between-group difference were examined at T3 to assess persistence at 2 months.

Statistical analyses were conducted using SAS Version 9.1 (SAS Institute Inc., Cary, NC) and IBM SPSS Statistics Version 22.

Results

Sample characteristics and intervention participation

We screened 129 women by telephone (Figure 1) between January 2012 and April 2013. Seventy-two women were eligible, of whom 48 were interested and were enrolled (CR, $n = 32$; WL, $n = 16$) across five separate cohorts (three to eight per intervention group). Recruitment was stopped early because of challenges in continued recruitment of subjects for the study. Table 1 shows demographic and medical variables, as well as WTAR, BDI-II, PAOFI and RAVLT scores at baseline. Groups did not differ significantly on baseline variables with the exception that the intervention group participants were more likely to be employed full time ($p = .05$), and this was controlled for in subsequent analyses. Of the 32 women assigned to the intervention, 2 withdrew before the first class began because of conflicting schedules and an additional woman withdrew after attending one group session. All of these women were included in the subsequent intent-to-treat analyses. For the remaining 29 women assigned to the CR group, 19 attended all five sessions (66%) and 9 attended four of the five sessions (31%) with 1 attending only three sessions. There were no makeup sessions; however, participants could follow any missed topics in the manual.

Cognitive complaints and neurocognitive assessments at baseline

Table 1 provides the baseline PAOFI and RAVLT assessments at baseline for the CR and WL groups. There were

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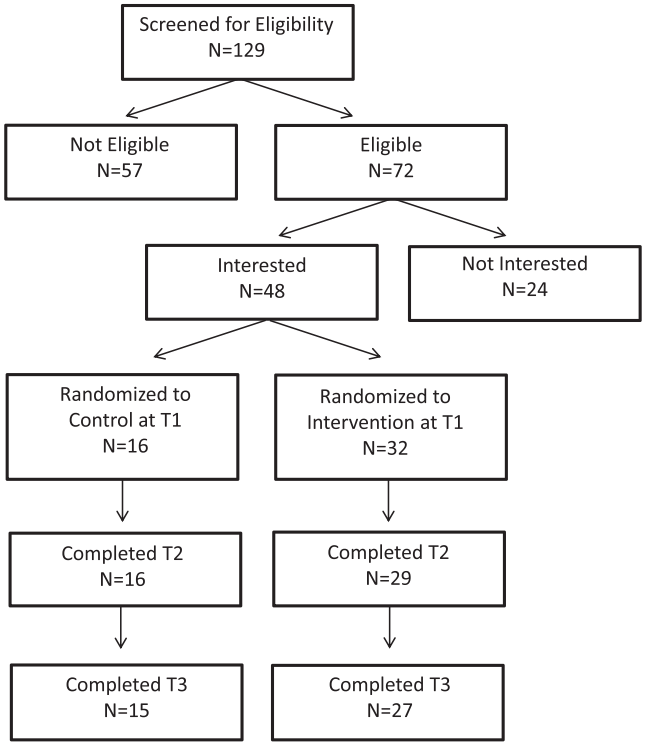

Figure 1. This diagram describes the flow of patients from recruitment through intervention and follow-up

no differences in the total PAOFI or PAOFI memory scores, and these scores were significantly increased compared with a normative non-cancer comparison group we have reported on earlier [29], documenting the severity of cognitive complaints in the participants recruited for this study. The unadjusted raw scores for the neurocognitive assessment battery are also shown in a supplementary table accompanying this article.

Evaluation of intervention outcomes

The primary outcome for this trial was the difference in PAOFI total score comparing the CR group to the WL control group. As can be seen in Figure 2A, the overall group difference was statistically significant with $p = .01$. In secondary analyses, we examined the impact of the intervention on the PAOFI memory scale score, and this was also significant for an intervention effect ($p = .01$). ES for changes from T1 to T3 for the intervention group were .90 for total and 1.10 for memory. For the control group, ES were .15 for total and .14 for memory.

We next explored the impact of the intervention on the RAVLT scores (Figure 2B). We found a significant overall group difference over time for RAVLT total (trials I–V) ($p = .02$) and RAVLT delayed recall ($p = .007$). For the intervention group, ES for changes from T1 to T3 were .57 for RAVLT trials I–V and .29 for delayed recall; and, for the control group, the ES were in the negative direction, at .30 and .82, respectively. Both groups showed significant improvement in the BDI-II scores (approximately 4-point reduction) at T2 and T3, with no significant difference between the two groups (data not shown).

Table 1. Selected baseline (T1) medical and demographic variables, and unadjusted key outcome scores

Variable	Intervention group $n = 32$	Wait list control group $n = 16$	Whole group $n = 48$	p-value[a]
Age	54.5 (7.0)	52.4 (10.1)	53.8 (8.2)	.40
Race (p-value is for White vs not)				
White	28 (88%)	15 (94%)	43 (90%)	.65
Black	0 (0%)	1 (6%)	1 (2%)	
Asian	4 (12%)	0 (0%)	4 (8%)	
Hispanic	2 (6%)	0 (0%)	2 (4%)	.55
Married or committed relationship	25 (78%)	13 (81%)	38 (79%)	1.0
Education				
Less than college	7 (22%)	5 (31%)	12 (25%)	.21
College graduate	9 (28%)	1 (6%)	10 (21%)	
Post-college degree	16 (50%)	10 (63%)	26 (54%)	
Estimated IQ (WTAR)	114.1 (8.3)	113.2 (11.8)	113.8 (9.5)	.77
Employment				
Employed full time	14 (44%)	3 (19%)	17 (35%)	.05
Employed part time	7 (22%)	9 (56%)	16 (33%)	
Not employed	11 (34%)	4 (25%)	15 (31%)	
Medical characteristics				
Years since diagnosis	2.8 (1.1)	2.9 (1.1)	2.8 (1.1)	.64
Received chemotherapy	24 (75%)	13 (81%)	37 (77%)	.73
Received radiation	23 (72%)	13 (81%)	36 (75%)	.73
Received Herceptin	8 (26%)	4 (27%)	12 (26%)	1.0
Currently on endocrine therapy	20 (63%)	14 (88%)	34 (71%)	.10
Mean # of comorbid conditions	1.7 (1.5)	1.7 (1.3)	1.7 (1.4)	1.0
Beck Depression Inventory (BDI)	14.4 (7.3)	15.7 (6.2)	14.8 (6.9)	.54
Key outcomes (unadjusted data)				
PAOFI total score	12.4 (6.5)	12.9 (7.0)	12.5 (6.6)	.81
PAOFI memory score	5.3 (2.5)	5.9 (2.7)	5.5 (2.5)	.42
RAVLT trial I–V total z-score	0.9 (1.0)	0.8 (1.0)	0.9 (1.0)	.91*
RAVLT delayed recall list A z-score	0.5 (1.0)	0.7 (0.9)	0.6 (0.9)	.43*

WTAR, Wechsler Test of Adult Reading; RAVLT, Rey Auditory Verbal Learning Test; PAOFI, Patient's Assessment of Own Functioning Inventory.

*p-values for RAVLT scores control for IQ.

[a]p-values are the result of t-tests for continuous variables and chi-squared (or Fisher's exact) tests for categorical variables.

qEEG substudy outcomes

The qEEG substudy included 36 participants. Analyzable pre-intervention and post-intervention EEGs were obtained for 29 participants, 28 of whom completed

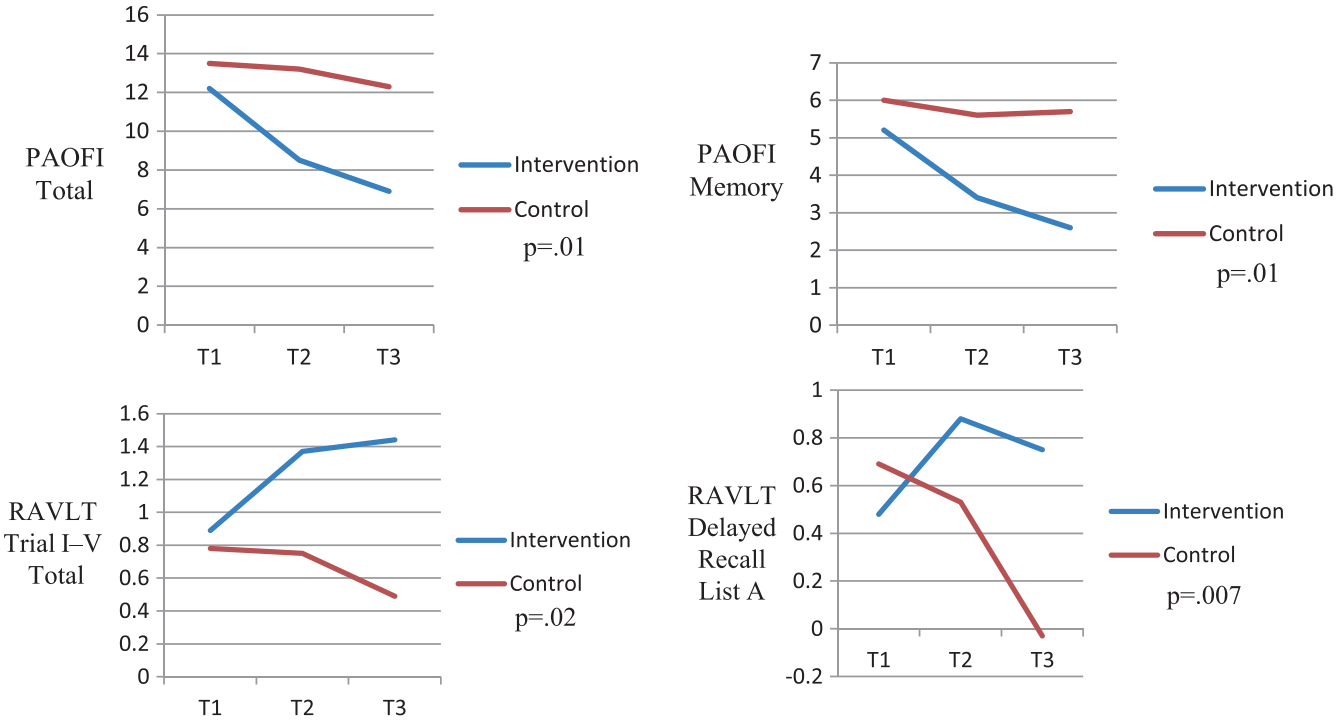

Figure 2. (A) Adjusted means from mixed models for Patients Assessment of Own Functioning Inventory (PAOFI) total and memory scale scores. (B) Adjusted means from mixed models for Rey Auditory Verbal Learning Test (RAVLT) for trial I–V and delayed recall list A z-scores

the PAOFI through T2 and 26 through T3. Women in the primary qEEG analyses ($n=28$) did not differ significantly on any demographic or medical variables or BDI-II scores in comparison with those who were not included ($n=20$).

CR versus WL groups differed significantly on T1-to-T2 changes in global absolute delta power ($t_{(27)}=-2.41$, $p=.02$) and the AP gradient of absolute alpha power ($t_{(27)}=2.12$, $p=.04$). Regarding delta power, the intervention group ($n=20$) showed a decrease of -10.35 (± 13.74) as compared with an increase of 3.14 (± 15.03) in controls ($n=9$) (Figure 3). The CR decrease in delta power at T2 did not predict PAOFI improvement at T2 ($p=.971$) or T3 ($p=.919$). Change in delta at T3 did not differ significantly between intervention (-5.18 ± 12.78) and WL (-7.26 ± 9.83) groups ($t_{(20)}=.36$, $p=.72$). Regarding the alpha power AP gradient, CR and WL groups showed T2 changes of $.031 \pm .084$, and $-.034 \pm .053$, respectively. The AP gradient increase in the intervention group was not a significant predictor of improved PAOFI total complaints at T2 ($p=.137$, N.S.) but *was* a significant predictor of improved complaints at T3 ($p=.012$), even when controlling for age and IQ ($p=.011$). This biomarker did not predict improvement in the WL group at T2 ($p=.964$) or T3 ($p=.998$). At T3 follow up, change in the alpha AP gradient did not differ significantly between intervention ($-.008 \pm .075$) and WL ($-.025 \pm .066$) groups ($t_{(24)}=.58$, $p=.57$).

Discussion

We conducted the current RCT to determine the efficacy of our CR intervention program for BCS, targeting cognitive complaints. Secondarily, we explored whether objective neurocognitive test would track with the subjective complaints, while also examining the potential value of qEEG as a biomarker of brain neurophysiology. The primary outcome for the trial, the PAOFI total score, improved significantly with the intervention and the improvements were sustained at 2 months post-intervention, while there was no improvement in the WL control group. In a secondary examination of the PAOFI memory subscale, there was a similar pattern of subjective improvement in the CR group. Concurrent neurocognitive assessment of auditory verbal learning showed significantly improved learning and recall among the CR group in comparison with the WL control group.

Similar to the current study, several small group interventions for cancer survivors resulted in improved objective or self-reported cognition. Cherrier et al. [30] administered memory strategy workshops to 28 cancer survivors who received adjuvant chemotherapy. The intervention group showed significant baseline-to-post-treatment improvement in self-perceived cognitive impairments, complaints, quality of life and attention, with a trend for improved delayed recall. In a cognitive behavioral-based intervention, [31] 40 BCS were randomized to either cognitive behavioral sessions or a WL. The intervention group demonstrated

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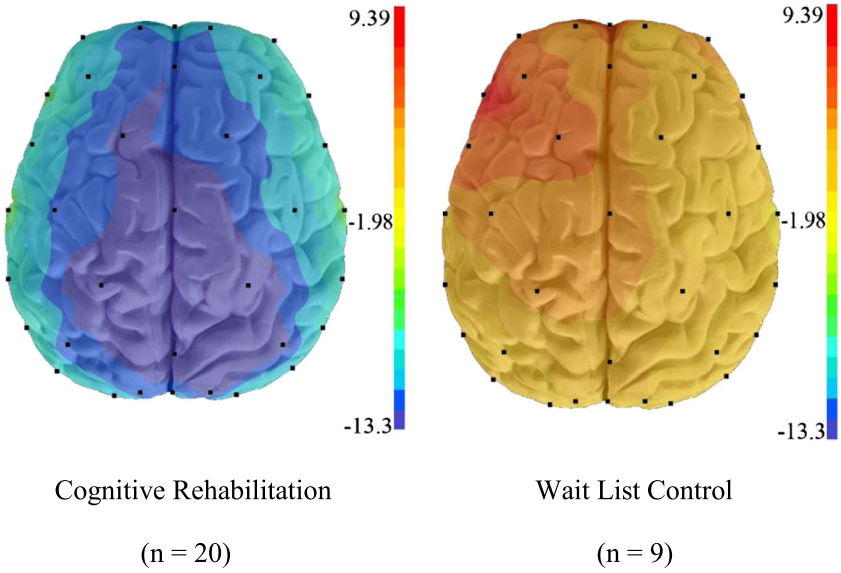

Figure 3. qEEG maps of delta power in cognitive rehabilitation and wait list control groups. CR participants ($n = 20$, left) showed large decreases in delta 'slow wave' power across the whole head compared with wait list controls ($n = 9$). The greatest decreases are shown in blue, increases are shown in red

significant improvements in verbal memory and quality of life but not for cognitive complaints. In a non-randomized feasibility study [32], a cognitive behavioral-cognitive training intervention was associated with immediate and 3-month sustained improvement in memory, psychomotor, visuospatial function and in some self-reported complaints in 23 cancer survivors compared with WL cancer survivor and non-cancer patient control groups. In two other randomized clinical trials for long-term cancer survivors, computerized training was shown to improve processing speed, memory or executive functions [33,34]. Taken together, these studies indicate that rehabilitation programs involving cognitive strategy training, cognitive behavioral interventions or computerized training can have benefits for objective attention/processing speed, memory and executive functions, and self-reported complaints. However, it should be noted that there are no active control group RCT published to date, but several approaches are being developed.

The qEEG substudy results provide some support for neurophysiological changes underlying the improvements in function associated with the cognitive intervention. We observed an overall decrease in delta 'slow wave' power and an increase in the frontal distribution of higher frequency (alpha) power over the 5-week CR intervention, which were not seen in WL controls. Further, the increased frontal alpha power was associated with decreased complaints at the 2-month follow-up suggesting that this measure may function as an early biomarker of later efficacy. Overall, these results comport with an 'aging' model of complaints [35] wherein 'slowing of the EEG' is seen generally in conditions of aging or cognitive dysfunction [36]. Our previous cross-sectional work found language and communication complaints associated with increased slow wave power (delta, theta) and overall cognitive complaints associated with decreased fast wave power (beta) [27]. In our prior CR feasibility study [8], improvement in complaints was associated with an increase in fast wave energy (alpha), although not specific to frontal regions.

The major limitations of this study are the small sample size, lack of an attention control group, and a homogeneous sample of BCS that limits generalizability to survivors of other types of cancer. We chose to examine the results from this phase II study prior to reaching the original target sample of 60, as there were challenges to assembling the groups for intervention and randomization, and we were uncertain of whether we could show evidence of any benefit. In spite of the smaller than planned study sample, we demonstrated a meaningful improvement in cognitive complaints as well as in the secondary outcomes. There was some imbalance in the baseline characteristics of the two groups, and this may have been related to the small sample and the 2:1 randomization. The WL group showed unexpected declines on recall scores, which may be an artifact of the small sample size, this particular sample, or reflect disadvantages of WL groups (e.g. lack of social or experimenter contact or lower test-taking motivation). However, in two studies of patients with cancer, women with the acute effects of chemotherapy and radiation therapy failed to show practice effects on memory tests [37,38]. Finally, the qEEG results should be interpreted cautiously as these exploratory findings were not corrected for multiple tests, and not all of the trial participants were included in the substudy because primarily of logistical reasons (e.g. scheduling).

In conclusion, this study demonstrated that a CR program for BCS improved both self-reported cognitive complaints and objective memory test performance, with

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benefits lasting up to 2 months following the intervention. Further, the qEEG substudy provides preliminary evidence of neurophysiological changes underlying the cognitive intervention and shows that changes in brain activity also coincide with reduced complaints. Future studies are needed to replicate these findings in a larger sample of cancer survivors, over longer follow-up periods, controlling for the social contact time and support that was part of the group intervention. Other biomarkers (e.g. inflammatory/genetic) for predicting individuals' responses to the rehabilitation intervention could be explored.

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Conflict of interest

The authors have declared no conflicts of interest.

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