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The Feasibility of Using Metacognitive Strategy Training to Improve Cognitive Performance and Neural Connectivity in Women with Chemotherapy-Induced Cognitive Impairment

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Key Words
Breast cancer · Metacognitive strategy training · Neuroimaging · Occupational therapy · Cancer survivorship

Abstract
Objective: To evaluate the feasibility and preliminary effect of metacognitive strategy training (MCST) on cognitive performance and on neural connectivity in the frontoparietal network in women with chemotherapy-induced cognitive impairment (CICI) following treatment for breast cancer. ***Methods:*** A single-group pre/post study was conducted. After completing the baseline assessment battery and neuroimaging, the participants completed a 12-session MCST intervention. Following the completion of the intervention, the subjects completed the same assessment battery and neuroimaging as was completed at baseline within 4 weeks after the intervention. The key inclusion/exclusion criteria for this study were: completed chemotherapy for treatment of breast cancer, no other neurological or psychiatric diagnoses, self-reported CICI, and no contraindications to the use of MRI. ***Results:*** MCST had a small-to-large positive effect on all primary (cognitive) and secondary (quality of life and psychosocial) behavioral outcome measures (r = –0.12 to –0.88). There was also a positive change in functional connectivity in a frontoparietal cognitive control network connection in 6 of the 10 subjects, which was correlated to changes in the behavioral measures. ***Conclusions:*** This study found that MCST was associated with a positive effect on cognitive performance and neural connectivity in women with CICI following treatment for breast cancer.

Introduction

Breast cancer is the most common malignancy in women with an estimated incidence of 234,840 in 2015, accounting for 29% of female cancer incidence in the USA [1]. The use of chemotherapy has led to significant improvements in survival in breast cancer patients [2, 3], and chemotherapy is administered to the majority of patients with early-stage disease to reduce the risk of recurrence [4]. In spite of the survival benefits, chemotherapy

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has been associated with decreased productivity, impaired community involvement, and poor role functioning resulting from cognitive dysfunctions following treatment [5–9]. Cancer survivors have cognitive deficits in several domains after chemotherapy, but most often in executive function (EF; planning, problem-solving, and multitasking). Women with such EF deficits following breast cancer treatment report changes in everyday life activities such as work/productivity, community involvement, driving, and financial management [5–9]. These cognitive changes are referred to as chemotherapy-induced cognitive impairments (CICI) or 'chemobrain'. The rates of CICI in the published literature range from 16 to 75% [10, 11].

Clinically, EF impairment related to CICI is most often identified using self-report measures and neuropsychological assessments; however, self-report measures do not provide an objective method to compare cognitive abilities between participants, and neuropsychological assessments have limited ability to capture real-world cognitive performance [12–15]. Noninvasive neuroimaging is a promising complementary assessment to identify deficits in EF associated with CICI, and a relatively new neuroimaging method being used for this purpose is resting-state functional connectivity MRI (rs-fcMRI). During rs-fcMRI, intrinsic brain activity is imaged when subjects are at wakeful rest and not performing a task, in order to understand the functional organization of the brain [16, 17]. Using rs-fcMRI, alterations in global and regional functional connectivity have been reported in breast cancer survivors [18, 19]. Using rs-fcMRI, our research team recently found that breast cancer survivors who report CICI, compared to those who do not, show weaker functional connectivity between two regions of the frontoparietal executive control network [20]. In addition, weaker functional connectivity correlated with higher levels of reported cognitive impairment [20].

There are two common interventional approaches to address cognitive impairment: the compensation model and the restoration model [21]. The premise of restoration-based methods is that through repetitive practice of cognitive retraining activities, overall cognitive performance will improve [21]. Recent clinical studies evaluating the use of restoration-based methods with cancer survivors, including breast cancer survivors, has found that these methods can improve cognitive function [22, 23]. Unfortunately, these studies and several others suggest that this restoration approach has little impact on everyday life performance [22–26]. In contrast to the restoration model, the compensation model includes interventions like metacognitive strategy training (MCST). MCST interventions tend to be targeted at the performance and participation level in order to help participants improve/learn new skills to complete everyday life activities, and they are usually delivered by occupational therapists. There is some existing evidence that suggests that MCST has more of a positive effect on EF impairments and activity performance than remediation-/retraining-based approaches [27].

One of the concepts and theories driving MCST is experience-dependent neuroplasticity, which postulates that learning new skills leads to functional changes in the brain [28]. Current evidence suggests that the MCST approach directly targets the action of the frontoparietal network, a cognitive control network involved in flexible moment-to-moment task control that also reflects compositional coding to enable the transfer of knowledge to novel tasks [29–31]. MCST approaches help individuals learn general strategies that they can employ in multiple contexts to improve their performance which requires flexible cognitive control and the ability to transfer knowledge to novel tasks [32].

Given the results of our preliminary study that showed the negative impact of CICI on this frontoparietal network and what is known about MCST [20], the purpose of this study was to evaluate the feasibility and preliminary effect of MCST on cognitive performance and on neural connectivity in the frontoparietal network in women with CICI following treatment for breast cancer.

Subjects and Methods

A single-group pre/post study was conducted. Participants were recruited from breast cancer patients in the clinical database at the Washington University Faculty Practice Plan Division of Breast Oncology at Washington University in St. Louis. This study was reviewed and approved by the Washington University Human Research Protection Office (HRPO) and the Protocol Review Monitoring Committee (PRMC) at the Siteman Cancer Center.

Participants

Participants were recruited from the Siteman Cancer Center at the Washington University School of Medicine. Inclusion criteria were: (1) females 35–70 years old; (2) self-reported CICI [global rating of cognitive dysfunction as 'moderately', 'strongly', or 'extremely' and a Cognitive Failures Questionnaire (CFQ) score >30]; (3) adjuvant (or neoadjuvant) chemotherapy completed at least 6 months prior to participation; (4) being able to read, write, and speak English fluently; (5) being able to provide valid informed consent; (6) having a life expectancy of more than 6 months at the time of enrollment; (7) females diagnosed with breast cancer (invasive ductal or lobular BrCA stage I, II, or III) and chemotherapy completed within the preceding 2 years, and (8) being on stable

doses (i.e., no changes in the previous 90 days) of medications that are known to impact cognitive function (i.e., antidepressants).

Exclusion criteria were: (1) prior cancer diagnoses at other sites with evidence of active disease within the previous year; (2) active diagnoses of any acute or chronic brain-related neurological conditions that can alter normal brain anatomy or function (e.g., Parkinson's disease, dementia, and cerebral infarcts); (3) severe depressive symptoms [a Personal Health Questionnaire (PHQ-9) score ≥21]; (4) a history of traumatic brain injury; (5) weighing over 350 pounds (weight limit of the MRI machine); (6) having received skull-based radiation treatment within the previous year for any reason; (7) implanted metal objects not compatible with MRI, electrodes, pacemakers, intracardiac lines, or medication pumps; (8) a history of claustrophobia or inability to lie flat that would preclude undergoing MRI; (9) any medical condition which would render the study unsafe or not in the best interest of the participant, and (10) male gender. The clinical coordinators in the breast oncology division identified female breast cancer patients based on criteria related to age, diagnosis, comorbidities, and language. The remaining inclusion/exclusion criteria were evaluated by the research coordinator.

No study of which we are aware has examined the effect of MCST for CICI at a brain network level of investigation. Therefore, effect sizes of alterations in cortical network correlations, which are required for sample size determination, are unknown. The purpose of this pilot study was to evaluate if MCST could have a measureable effect on subjective and objective cognitive performance and also on neural connectivity, as measured by rs-fcMRI. Based on the experience of the research team, a sample of 14 participants was determined as the minimum sample size necessary in a repeated-measures design to detect a change in signal in the neuroimaging data.

Assessment and Intervention Procedures

Breast cancer patients who received chemotherapy at the Siteman Cancer Center of the Washington University School of Medicine and met the inclusion/exclusion criteria of the study were identified, and their contact information was forwarded to our research team. Patients who were interested were asked to complete a screening battery over the phone or via a Web-based survey to evaluate their eligibility and identify if they had CICI (global rating of cognitive dysfunction as 'moderately', 'strongly', or 'extremely' and a CFQ score >30). The study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Washington University in St. Louis [33]. REDCap is a mature, secure, Web-based application designed to support data capture for research studies.

The patients with self-reported CICI were then scheduled for a face-to-face assessment to determine their final eligibility. After providing informed consent, eligible patients were asked to complete the baseline assessment battery and were scheduled for the neuroimaging assessment. After completing the baseline assessment battery and neuroimaging, the participants completed a 12-session (or until their goals were met) MCST intervention with a trained occupational therapist. Each session lasted 45 min and the intervention was completed over the course of 12–14 weeks. Participants may have had completed fewer sessions if they met their baseline goals before the completion of 12 sessions. Following the completion of the intervention, the subjects completed the same assessment battery and neuroimaging as was completed at baseline within 4 weeks after the intervention.

Intervention Description: Cognitive Orientation to Daily Occupational Performance – An MCST Treatment Approach

Cognitive Orientation to Daily Occupational Performance (CO-OP) is an MCST treatment approach that incorporates both global and domain-specific cognitive strategies [34]. Complete details about the CO-OP approach have been published previously [35]. CO-OP has seven key features: (1) cognitive strategy use, (2) patient-chosen goals, (3) dynamic performance analysis, (4) guided discovery, (5) enabling principles, (6) parent/significant other involvement, and (7) intervention format [34]. In the first meeting, the patient selects 3 activities to be the focus of treatment, and the baseline level of performance for each activity is established. In the second meeting, when CO-OP actually begins, the approach is introduced to the patient and the global cognitive strategy (goal-plan-do-check) is learned. In all subsequent sessions, this strategy is used as the main problem-solving framework to facilitate skill acquisition. The patient identifies a 'goal', and then is guided by the therapist to develop his/her own 'plan' to potentially achieve the goal. The client is then asked to 'do' the plan (if feasible during the therapy session, otherwise asked to complete at home prior to the next treatment session), and subsequently to 'check' to see if the plan worked – i.e., if the goal was achieved. If the goal was not achieved, as is often the case initially, the patient is guided to analyze what went wrong and to modify the plan. Thereby, the lack of success is associated with the wrong plan rather than a problem with his or her personal capacity. Throughout, the therapist actively seeks opportunities to promote the generalization of skills and strategies to the natural environment and transfer to novel skills.

Behavioral Outcome Measures

All participants completed the baseline assessment (approx. 90 min) with a blinded rater. The same assessment battery was used after the intervention. Table 1 provides an overview of all the behavioral outcome assessments. The primary outcome measures are subjective and objective measures of cognitive performance.

Neuroimaging Outcome Measurement

rs-fcMRI and anatomical images were collected using a Siemens 3T Tim Trio MRI scanner. The anatomical T1-weighted magnetization-prepared rapid gradient echo (MP-RAGE) image was acquired across 176 sagittal slices [TR = 2,400 ms; TE = 3.09 ms; flip angle = 8°; inversion time (TI) = 1,000 ms; 1 × 1 × 1 mm voxels]. An asymmetric spin-echo echo-planar pulse sequence [by echo-planar imaging (EPI); TR = 2,200 ms, TE = 27 ms; flip angle = 90°; 4 × 4 × 4 mm voxels] captured images of blood oxygenation level-dependent (BOLD) contrast responses across 36 odd-even, contiguously interleaved, bicommissurally aligned axial slices [36, 37]. Three 164-frame (6-min) EPI runs recorded spontaneous brain activity while participants were awake, not performing a task, with their eyes open in a darkened room.

Image Preprocessing

EPI image preprocessing started with compensation for systematic slice-dependent differences from interleaved odd-even slice acquisition and alignment of the time for each slice to the beginning of each volume acquisition using sinc interpolation. Next, corrections for intensity differences within runs utilized a whole-brain mean signal intensity normalized to mode 1000. These time- and intensity-adjusted slices were realigned within and across runs

Table 1. Baseline assessment battery

Measures	Description
Primary outcome measures	
Cognitive Failures Questionnaire (CFQ) [58]	The CFQ measures subjective lapses in motor function, memory, and perception; this questionnaire contains 25 items and scores range from 0 to 100
Dysexecutive Questionnaire (DEX) [59]	The DEX measures behavioral changes associated with having executive dysfunction; the questionnaire contains 20 items
Delis-Kaplan Executive Function System (DKEFS) [60] – Trailmaking Subtest	The DKEFS is the only objective, scaled EF battery available; it has 9 stand-alone tests; the Trailmaking Condition 4 subtest score was used, which measures cognitive flexibility
Secondary outcome measures	
PROMIS-57 Profile v1.0 [61]	The PROMIS measures subjective changes in physical function, fatigue, and satisfaction with social roles
Canadian Occupational Performance Measure (COPM) [62]	The COPM measures changes in performance of tasks by measuring the clients' perceived performance and satisfaction with their level of participation
Personal Health Questionnaire (PHQ-9) – Depression [63]	The PHQ-9 measures depressive symptoms
Montreal Cognitive Assessment (MoCA) [64]	The MoCA measures general cognitive status; it is a publicly available screening tool used to screen for dementia
Self-Efficacy Gauge (SEG) [65]	The SEG measures an individual's confidence in everyday life activities

using rigid body correction for interframe head motion [38–41]. The across-run-realigned slices were resampled to 3-mm^3 voxels and registered to an atlas template by computing 12 parameter affine transforms between an average from the first frames of each EPI run and the atlas template using the individual's MP-RAGE image as an intermediary [42]. This atlas template was created using MP-RAGE structural images from 12 normal middle-aged individuals (mean 48 years, SD ±10.7) and registered to Talairach atlas space [43, 44] based on spatial normalization methods [45]. Each subject's second scan was cross-day realigned to the MP-RAGE of the first scan.

For rs-fcMRI analyses, additional preprocessing steps were applied in MATLAB (2012a; The MathWorks, Natick, Mass., USA) to reduce noise from sources unlikely to reflect neural activity [46]. These steps included demeaning and detrending each BOLD run, temporal filtering with a bandpass filter to remove frequencies <0.009 Hz and >0.08 Hz, and spatial smoothing with a 6-mm full-width-at-half-maximum Gaussian kernel. Using linear regression, the BOLD signal per voxel was adjusted for 24 motion-related and 6 tissue-related sources of nuisance variance. The motion regressors are the 6 previously computed linear corrections for head movement, their squares, and the same for the immediately preceding time point, as derived by Volterra expansion [32]. The tissue-related regressors were a global whole-brain signal averaged over all voxels, signals in the ventricles and white matter, and their associated temporal derivatives [47]. The subject's own anatomy, as segmented using FreeSurfer version 5 [48], was used for whole-brain, ventricle, and white matter masks [39, 40, 49, 50]. We applied a volume censoring method [46] which removed frames of data with >0.3 mm of frame-by-frame displacement, as well as episodes with fewer than 5 contiguous frames with <0.3 mm of frame-by-frame displacement [51]. In addition, BOLD runs with fewer than 30 frames meeting these requirements were eliminated. Only the 10 subjects with 119 or more frames of good data in both scans were retained for analysis. Spatial smoothing and temporal filtering as well as nuisance variable regression were repeated on the original preprocessed data, leaving out the censored frames and interpolating across the gap [52]. Since the motion correction parameters used were more lenient than recommended, we plotted the difference between scan days in each region pair correlation versus the distance between regions for 264 regions sampling the entire brain [16] to check for the distance-dependent artifact often caused by even submillimeter head motion [46, 53].

Table 2. Characteristics of the study sample (n = 14)

Median age (min.–max.), years	50.50 (36–65)
Median time since completion of chemotherapy (min.–max.), months	9.5 (7–34)
Race	
Caucasian	12 (86%)
African-American	1 (7%)
Asian	1 (7%)
Highest level of education	
High school or associate degree	2 (14%)
Bachelor's degree	3 (21%)
Master's or doctoral degree	9 (65%)
Work status	
Full time	12 (86%)
Part time	1 (7%)
Retired	1 (7%)

Table 3. Behavioral outcomes

Assessment	Pre-intervention score	Post-intervention score	Median of difference pre-post (95% CI)	Effect size r[a]	Interpretation
Primary outcome measures					
CFQ	50 (39–68)	36 (15–49)	15 (8.9 to 25.2)	–0.85	Decrease in subjective cognitive symptoms
DKEFS – Trailmaking Condition 4	12 (1–13)	12 (7–14)	–1 (–2.1 to 0)	–0.50	Improvement in objective EF (cognitive flexibility)
DEX	23 (3–39)	11 (0–33)	9 (4 to 16)	–0.75	Improvement in subjective executive performance
Secondary outcome measures					
MoCA	28 (21–30)	28 (21–30)	0 (–1.05 to 0.05)	–0.28	Stable general cognitive function
COPM	4.8 (2.6–7.3)	7.7 (5.8–9.7)	–3 (–3.3 to –1.6)	–0.88	Improvement in self-rated performance of activities
	2.8 (1.4–5.5)	8.0 (3.5–10.0)	–4.5 (–5.3 to –3.3)	–0.88	Improvement in self-rated satisfaction with performance of activities
PHQ-9 – Depression	6.5 (1–13)	4.5 (0–11.0)	1.5 (0.9 to 4.1)	–0.53	Decrease in depressive symptoms approaching significance
NIH PROMIS-57 – Physical Function	25.8 (20.2–37.5)	24.7 (20.2–32.7)	3.6 (2.9 to 4.8)	–0.88	Improvement in self-reported physical function
NIH PROMIS-57 – Anxiety	53.8 (37.1–61.4)	45.9 (37.1–61.4)	0 (–0.1 to 9.0)	–0.65	Decrease in reported anxiety symptoms
NIH PROMIS-57 – Depression	44.7 (38.2–59.4)	44.7 (38.2–56.8)	2.3 (0 to 9.3)	–0.53	Decrease in reported depression symptoms
NIH PROMIS-57 – Fatigue	51.5 (41.1–65.3)	52.0 (33.1–58.5)	7.9 (1.6 to 10.7)	–0.70	Decrease in fatigue symptoms
NIH PROMIS-57 – Sleep Function	50.2 (30.5–63.0)	49.0 (30.5–63.0)	0 (–2.9 to 5.3)	–0.12	No change in sleep function
NIH PROMIS-57 – Satisfaction with Participation in Social Roles	45.3 (37.7–65.6)	53.4 (41.0–65.6)	–3.8 (–10.0 to 0)	–0.67	Improvement in satisfaction with participation
NIH PROMIS-57 – Pain Interference	48.9 (40.7–62.8)	56.6 (40.7–67.7)	–1.25 (–15.9 to 3.5)	–0.30	Increase in pain interference

Pre- and post-intervention scores are expressed as medians (min.–max.). [a] Effect size r: 0.1 = small effect; 0.3 = medium effect; 0.5 = large effect [55].

Analysis

Feasibility data were analyzed using descriptive statistics. Behavioral data analysis was conducted using SPSS version 20 [54]. The data were cleaned and checked for accuracy. The data were found not to be normally distributed; thus, nonparametric analysis methods were used. Distributions of the scores for each of the tests before and after the intervention are described using medians and ranges. The difference between pre- and post-test scores was calculated for each subject for each test. The median of the difference and 95% CI was calculated using the Student version of MINITAB® release 14.11.1. The Wilcoxon signed-rank test was used to test for significant differences in pre-post test scores. Nonparametric effect size (r) calculations were also performed on the behavioral data [55].

For neuroimaging data analysis, time courses were calculated for each subject and each scan for the two frontoparietal control regions which showed a difference between impaired and non-impaired breast cancer survivors [20], and also for 264 regions covering the brain [16]. Fisher z-transformed Pearson correlation coefficients calculated between two regions' time courses in a single scan served as a measure of functional connectivity between them. The Fisher z-transform normalizes the distribution of values to satisfy the assumptions of Student's t test and comparisons using the Gibbs distribution. Functional connectivity across the brain was compared between days using object-oriented data analysis [56], which uses an iterative approach and comparison to the Gibbs distribution to assess the significance of differences found in a multidimensional approach. Spearman's rho correlations were also calculated to evaluate the relationship between the changes in functional connectivity in the previously reported connection [20] and changes in the behavioral outcome measures.

Results

Feasibility

Based on the initial inclusion/exclusion criteria related to age, gender, and diagnosis, 127 women were referred to our study. From this sample, 72 women either did not report having CICI symptoms or did not show up for their scheduled testing. Another 38 women could not be reached via the contact information they had listed in their medical record. The remaining 17 women started treatment and 14 completed treatment; on average, those who completed the intervention completed an average of 9.79 (SD 2.04) sessions. Therefore, our recruitment rate was 13.4% of our potential sample of

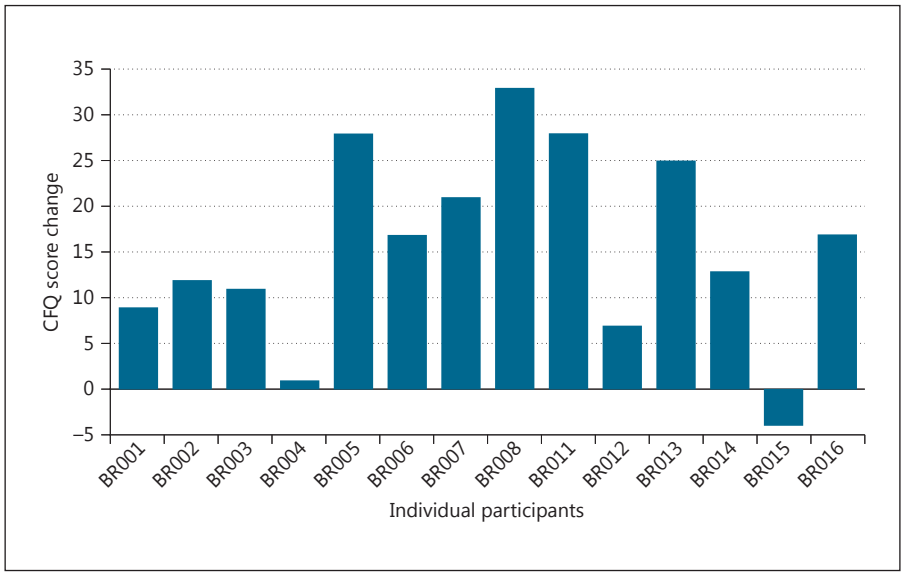

Fig. 1. Change in CFQ score between before and after treatment.

breast cancer survivors; however, it was already anticipated that only a certain percentage of this sample would meet the criterion of having CICI. Our attrition rate was 17.6%. Due to the small sample, no comparisons were made to determine if the 3 women who did not complete the study differed from the remaining sample. One woman dropped out after active disease had been found during a follow-up appointment, and the remaining 2 women dropped out secondary to conflicts with work schedules.

Participants' Results

Our sample is described in table 2. Overall, our sample was fairly young, well educated, mostly Caucasian, and mostly working full time during their participation in this study. The median time elapsed since the completion of chemotherapy was slightly less than 12 months.

Behavioral Results

Table 3 displays the distribution of the data for the behavioral outcome measures as well as the distribution of differences in scores before as compared to after the intervention. The results show that CO-OP had a medium-to-very-large effect on all the primary and secondary behavioral outcome measures in our sample (n = 14) with the exception of sleep function.

Given the limited sample size, the individual effect of the intervention on the CFQ was also qualitatively evaluated and plotted in a bar graph in figure 1. As depicted in figure 1, there was evident variation in terms of response to the CO-OP intervention on this subjective outcome measure; however, the majority of the participants had improvements in their subjective score on the CFQ (a positive change on the CFQ indicated improved cognitive function).

Neuroimaging Results

Ten of the 14 subjects had a sufficient number of good frames of MRI data in both pre- and post-treatment scans to be analyzed further. The amount of data kept did not differ between the two scans (paired t test: $p = 0.59$). The plot of change in functional connectivity between scans versus the distance between regions for the 264 regions showed no distance-dependent artifact, justifying the use of slightly relaxed motion parameters to include more subjects.

Object-oriented data analysis [56] for comparing subjects before and after treatment across all 264 regions was not sensitive enough to detect a difference in functional connectivity ($p = 0.79$). However, a one-tailed, paired t test on the connection between the two frontoparietal control regions previously described [20] showed trend-level significance ($p = 0.054$), demonstrating the expected increase in the strength of functional connectivity after treatment in 6 of the 10 subjects, as well as minimal decreases in 3 others (fig. 2).

The change score (post- minus pre-intervention score) in the PHQ-9 correlated strongly ($r_s = 0.663$) with the change in connection strength between the frontoparietal regions evaluated. Additionally, both the DKEFS – Trail-

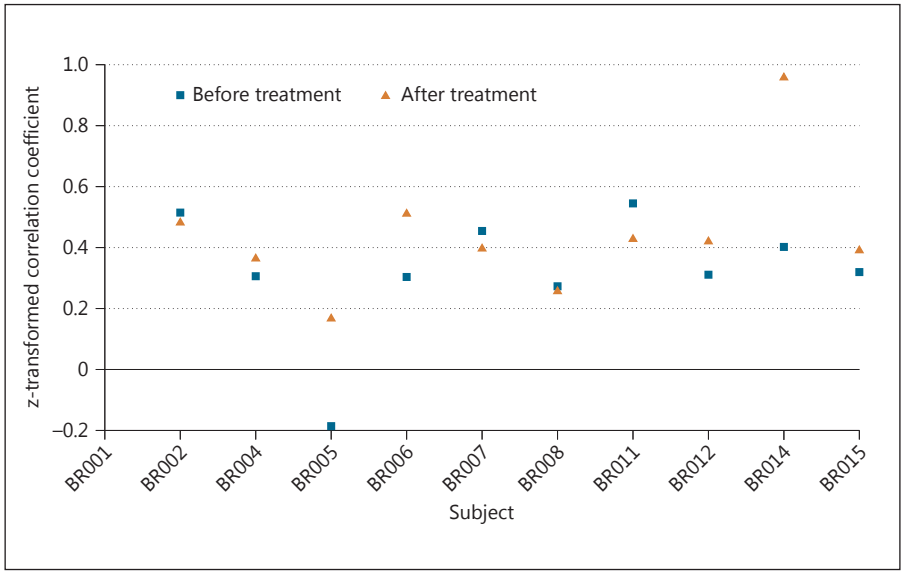

Fig. 2. Connection strength before and after treatment.

making Condition 4 (r_s = –0.0369) and the DEX (r_s = 0.596) change scores correlated moderately with the change in connection strength between the frontoparietal regions evaluated. Finally, there was a measureable but weak correlation between the CFQ change score and the change in connection strength between the frontoparietal regions evaluated (r_s = 0.201).

Discussion

The results from this study suggest that the use of CO-OP is feasible with this population. Overall, our recruitment and retention rates were acceptable and along with self-report outcome measures demonstrate that the women in this study found value in the intervention. CO-OP was also associated with a positive effect by improving subjective and objective cognitive performance, subjective activity performance, and quality of life. Further, we were able to measure a positive change in functional connectivity in the one frontoparietal cognitive control brain network connection previously reported on [20], and this change was correlated with changes in a few of the behavioral measures. The results from the study are consistent with previous work using CO-OP in individuals with cognitive deficits following stroke that found positive changes in activity performance and satisfaction [57] and also changes in objective cognitive performance [27]. This study, however, is the first to evaluate the effect on a particular brain system, i.e., the frontoparietal cognitive control network, of using CO-OP to address CICI. Given the limitations in how EF is often measured clinically, these data provide support for continued investigation into the use of functional neuroimaging as an objective way to assess mechanistic changes in higher-level cognitive function in women with CICI.

An important strength of the study is its repeated-measures, within-patient design. However, the study had several limitations. First, while a single-group pre/post study was appropriate for this early-stage investigation, the lack of an active control group for comparison limits the ability to conclude the changes we observed were due to the intervention and not due to other nonspecific effects of CO-OP or other factors, e.g, the passage of time and/or a learning effect. The next phase of this investigation should include an active control group to confirm the effects identified in this study were due to the CO-OP intervention. Second, the sample had substantial heterogeneity in terms of age, time since the completion of chemotherapy, and differences in response to the intervention on both the behavioral and neuroimaging measures. As shown in figure 2, some individuals had an over 30-point reduction in reported cognitive problems after the intervention, while 1 person actually had a 4-point increase in reported cognitive problems. The present study provides data to inform the sample size for future studies, which must enroll a sufficient number of subjects to control for differences in response and better identify the responders versus the

nonresponders to the intervention. Also, the self-report outcomes measures of cognitive function used in this study – i.e., the CFQ and DEX – have limited psychometric development, which needs to be addressed in future studies. Finally, while functional neuroimaging was able to detect a positive change in functional connectivity in 6 of the 10 subjects, the use of resting-state functional connectivity as an outcome measure was exploratory and needs considerable further investigation to evaluate its utility as a measure of the mechanistic action of CO-OP.

While there are several methodological and design limitations to this pilot study, its results do support continued investigation into CO-OP for women with cognitive impairment after chemotherapy for breast cancer. Future studies need to examine the findings of this study with an active control group and an attempt to control for the confounding factors (e.g., hormonal treatment, different chemotherapy treatment regimens, etc.) that may have influenced the results of this study. Overall, this study found that the use of an MCST intervention (CO-OP) is associated with a positive effect on patient outcomes and functional connectivity in a cognitive control network previously demonstrated to be negatively impacted after chemotherapy for breast cancer [20].

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Disclosure Statement

The authors have no conflicts of interest to report.

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