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SI: NEUROIMAGING STUDIES OF CANCER AND CANCER TREATMENT

Assessment of the feasibility of a rehabilitation intervention program for breast cancer survivors with cognitive complaints

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Abstract To assess the feasibility of a cognitive rehabilitation program in breast cancer survivors (BCS) with persistent post-treatment cognitive complaints. BCS with cognitive complaints, 18-months to 5-years post-treatment, were recruited for a once-weekly, five-week, group cognitive training intervention. Outcome measures included self-reported mood and cognitive function, and neurocognitive tests administered at pre-intervention, immediate-, two-month and four-month post-intervention. A sub-study in eight participants evaluated resting state quantitative electroencephalography (qEEG) changes from pre- to immediate post-intervention in relationship to post-intervention changes in cognitive complaints. Twenty-seven BCS completed the protocol and tolerated the intervention well. We observed significant reductions in total and memory-specific cognitive complaints from pre-intervention to immediate post-intervention (p=0.031 and p=0.009, respectively) and at four-months post-intervention (p<0.0001 and p<0.001, respectively). Significant improvement in neurocognitive tests were found for Symbol Digit, Stroop, and Trails A tests (df=26, all p's <0.05). Effect sizes for changes from pre-intervention to immediate and to four-month post intervention ranged from 0.429 to 0.607, and from 0.439 to 0.741, respectively. Increase in qEEG absolute alpha power over the course of the intervention was associated with reduced complaints at immediate post-intervention (r=−0.78, p=0.021), two-months (r range= −0.76 to −0.82, p-value range 0.004 to 0.03), and four-months (r=−0.71, p=0.048). A five-week group cognitive training intervention is feasible and well tolerated. Cognitive complaints and neurocognitive test performances showed positive changes. qEEG may serve as a potential biomarker for improvement in self-reported complaints. A randomized clinical trial is underway to test the efficacy of the intervention.

Keywords Breast cancer · Chemotherapy · Cognitive · qEEG · Rehabilitation · Intervention

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Introduction

Subjective cognitive complaints are common both during and after cancer treatments (Ferguson and Ahles 2003; Tannock et al. 2004; Vardy et al. 2008; Boykoff et al. 2009). Post-treatment cognitive complaints in breast cancer survivors (BCS) have been increasingly noted because the majority of women with breast cancer diagnosed today achieve long-term survival (Jemal et al. 2009), and cognitive dysfunction can limit their return to pre-illness activities. Many BCS exposed to adjuvant chemo- and hormonal therapies complain of decreased cognitive efficiency that has often been attributed to chemotherapy, colloquially termed "chemo brain." These complaints are also associated with endocrine therapies such as tamoxifen (Hurria et al. 2007; Schilder et al. 2010); however, the true etiology is likely far more complex (Ahles and Saykin 2007). Up to 35 % of post-treatment BCS complain of persistent and sometimes disabling cognitive difficulties (Ahles and Saykin 2007; Janelsins et al. 2011; Reid-Arndt et al. 2009; Wefel et al. 2004; Wefel and Schagen 2012), yet these impairments are not consistently measureable with neurocognitive tests (Castellon et al. 2004; Cull et al. 1996; Schagen et al. 2002). Some BCS may perform normally on neurocognitive tests, while others show variable deficits for verbal and nonverbal memory, visuospatial, attention and executive functions (Ahles et al. 2002, 2010; Janelsins et al. 2011; Jim et al. 2012; Schagen et al. 2007; Vardy et al. 2007; Wefel and Schagen 2012). It therefore is necessary both to develop interventions for cognitive complaints in BCS, and to develop reliable methods for measuring the efficacy of these interventions.

In 2008, when we began the development and pilot-testing of a group-based cognitive rehabilitation intervention program for BCS that we describe in this report, there were few efforts underway to address this post-treatment problem. Since that time, early studies of either cognitive behavioral therapy or psycho-education with cognitive training have reported encouraging results (Ferguson et al. 2007, 2012; Poppelreuter et al. 2009; Schuurs and Green 2012; Von Ah et al. 2012). In this paper we present descriptive information about the UCLA Cognitive Rehabilitation Intervention Program for BCS with cognitive complaints, focusing on the feasibility of delivering the intervention in the target population, and examining the potential benefits of the program with regard to both self-reported cognitive function and neuropsychological test outcomes. In addition, this report includes pilot data on the use of quantitative electroencephalography (qEEG) in a sub-group of participants to explore its potential use as a biomarker of intervention benefit. These initial studies were used to provide support for a subsequent randomized trial that is currently underway.

Methods

Participant recruitment and eligibility

BCS were recruited from local newspaper ads, flyers and community talks and from our survivorship center program. Inclusion criteria included: 1) age 21 to 75 years; 2) stage 0, I, II, III female breast cancer survivors who were within 18 months to 5 years after completion of initial primary treatments with surgery, radiation and/or chemotherapy; 3) allowed to be on endocrine therapy and/or HER2 targeted adjuvant therapy; 4) able to read and speak English; 5) self-reported cognitive difficulties that interfered with everyday activities; 6) able to attend the consecutive five-week intervention meetings; 7) able to provide written informed consent. Telephone screening for eligibility included the following questions for determining sufficient cognitive difficulties: "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?" Affirmative responses were required of all three questions for study entry. Exclusion criteria included: 1) untreated current major depression determined using a screening measure (Burnam et al. 1988); 2) other current psychiatric disorder; 3) history of central nervous system (CNS) disease, CNS radiation, intrathecal chemotherapy, or CNS-involved surgery; 4) history of head trauma, seizure disorder, learning disability, or regular and heavy use of illicit substances consistent with possible substance disorder. Women recruited to the last cohort of participants were also invited to enroll in the qEEG sub-study to assess neurophysiologic changes in brain function (see below). The entire research protocol was approved by the UCLA IRB and all participants provided written informed consent before entering the study.

Overall design of the intervention and outcome assessment

Participants underwent neurocognitive testing and completed self-report questionnaires about mood and cognition at pre-intervention, immediately post-intervention (i.e., within a week of completing the intervention), 2 months, and 4 months following the completion of the intervention. Cognitive testing was conducted by a technician trained and supervised by a licensed neuropsychologist. The intervention was a manualized program with teaching materials for the participants (see below) and was delivered over five consecutive weeks by the same clinician. There were five separate cohort groups that received the intervention with group membership ranging from 4 to 9 women. The qEEG sub-study was conducted during the last cohort.

Description of the intervention program and procedures

Cognitive training The five-week intervention program is rooted in evidence-based cognitive rehabilitation and targeted attention, executive and memory challenges. Each session was 2 h in duration guided by an intervention manual developed for the program. The intervention included in-class and homework exercises and goal setting (Levine et al. 2000; Moore Sohlberg and Mateer 2001; Rogers and Monsell 1995; O'Brien et al. 2008; Verhaeghen et al. 1992; White and Shah 2006; Wilson 2003). Homework had three difficulty levels (Moore Sohlberg and Mateer 2001; Wilson 2003). Each participant received a training manual workbook with homework exercises, CDs for auditory exercises, answer keys, and a stopwatch for timing when needed. To facilitate the use of strategies for challenges at home or at work, participants were assigned homework relevant to daily life, as well as exercises not discussed in class, and were asked to set goals specific to daily life tasks that they needed to accomplish (Cavallini et al. 2003, 2010; Lustig et al. 2009; Turner and Levine 2004). The first 2 weeks of the intervention emphasized attention strategies; weeks three through five addressed executive functions, memory and a review, respectively. In each session, participants performed level I (easiest) and level II (moderate difficulty) exercises in class to provide mastery experiences, and received encouragement and support, engendering confidence and the familiarity with the process that would provide a sense that they could now do their homework. We suggested that women not overwhelm themselves with or pressure themselves with long homework sessions, as most of the women in the groups tended to be overloaded in their daily lives. Rather, we instructed them to follow a self-paced approach and to start with level I exercises first and if they could do several of these feeling comfortable and with greater ease, move to level II and so forth. We explained the importance of distributed practice rather than 'cramming' homework, and suggested attempting four 20-minute sessions per week of homework. They could do more if they chose. Group participants were asked to track their homework practice on a log that was provided for them. We were very careful not to reinforce or recreate in the participants a sense of pressure, proneness to failure, or engender any frustrations that the participants reported that they already experience in their daily life. Thus, our approach was one of being directive, while reinforcing each participant to learn about her areas of strengths and weaknesses, with a goal of balancing challenges in the exercises while minimizing frustration. The intervention focused on Attention, Executive functioning, and Memory domains, and is described in detail in the Appendix.

Revision The intervention underwent one revision after an initial cohort completed the intervention program. Originally, the intervention was six weeks long and included a segment on visuospatial function (i.e. exercises focused on finding a car in a parking lot, using a map to find stores in a shopping mall, and some mental rotation items). We eliminated this section based on feedback from the participants that this group session and the corresponding homework were not challenging—the majority of participants completed the assignments with ease. Similarly, we eliminated some executive function exercises that also were not challenging, per participants' reports. The eliminated exercises focused on filling out catalogue order forms for supplies and clothing. Again, participants did not find this challenging nor did they complain of having problems, for instance, with ordering merchandise online. The final version of the intervention then, included only the five sessions with exercises that the participants found sufficiently challenging

Outcome measures

Neurocognitive tests We identified a priori 16 neurocognitive tests most salient for the current study (Table 1). We administered a 90-minute battery of paper-and-pencil and computerized tests assessing verbal and visual memory, attention, executive and visuospatial functioning, and processing speed at each time point. Alternate forms were available for the Brief Visual Memory Test-Revised (Benedict 1997) and the Hopkins Verbal Learning Test-Revised (Brandt and Benedict 2001) (both with four alternate forms), and the Benton Judgment of Line Orientation test (Benton et al. 1994) (two forms). The order of alternate forms was not counterbalanced. The computerized CNS Vital Signs (Gualtieri and Johnson 2006) measures did not have alternate forms but they have a quasi-random order stimuli presentation. No alternate forms were available for Trailmaking tests (Spreen and Strauss 1998) or the Paced Auditory Serial Addition Test (Gronwall 1977). Higher scores indicate better performances.

Table 1 Neuropsychological test battery and scores

CNS Vital Signs Computerized Testing Platform
- Finger Tapping Dominant, Finger Tapping Non-Dominant
- Shifting Attention Test (correct)
- Stroop Reaction Time (simple, complex and number correct scores)
- Continuous Performance Test (correct)
- Symbol Digit Test (correct)
Hopkins Verbal Learning Test, Revised (total recall, delayed recall)
Brief Visuospatial Memory Test, Revised (total, learning slope)
Trailmaking Test, Part A (completion time)
Trailmaking Test, Part B (completion time)
Paced Auditory Serial Addition Test, Trial 1 (total errors)
Judgment of Line Orientation Test (total correct)

Self-reported cognitive function Participants completed the Patient's Assessment of Own Functioning Inventory (PAOFI, Chelune et al. 1986), a 33-item scale assessing self-perceptions of daily life cognitive difficulties in four domains: memory, language and communication, motor and sensory-perceptual function, and higher-level (executive) cognitive functions (HLC). The PAOFI yields a score for each cognitive domain and a total score. Higher scores indicate more complaints. The total score (range 0–33) was the main outcome of interest, but the memory and HLC subscales were also examined based on a priori hypotheses related to these domains (Ganz et al. 2013).

Self-reported mood state We administered the Beck Depression Inventory, 2nd Edition (BDI-II, Beck et al. 1996), and the Spielberger State-Trait Anxiety Inventory (STAI, Spielberger et al. 1971) to assess self-reported depression and anxiety, respectively.

qEEG procedures

Resting state EEG recordings were conducted in a manner similar to that employed clinically. Participants rested in the eyes-closed, maximally alert state in a sound-attenuated room with subdued lighting. Thirty-five Ag/AgCl electrodes were positioned with an electrode cap (ElectroCap, Inc.; Eaton, OH) according to an extended International 10–20 System with linked ears reference. Participants were alerted frequently to avoid drowsiness, and were instructed to remain still and inhibit blinks or eye movements during each recording period. Electrode impedances were balanced and were maintained below 5kΩ for all channels. Vertical and horizontal electrooculograms (EOG) were recorded to identify eye movement artifact using bipolar electrodes placed at the supraorbital and infraorbital ridges of the right eye and at the outer canthi of the left and right eyes. A minimum of 10 min of EEG data were recorded using a 22-bit resolution Neuroscan 4.3 system at a sampling rate of 256 Hz, with a high-frequency filter of 70 Hz, a low-frequency filter of 0.3 Hz, and a notch filter at 60 Hz. Data were stored in digital format and imported into Brain Vision Analyzer (BVA) software (Brain Products GmbH; Gilching, Germany) to remove offsets, optimize scaling, and segment the data into 2-second non-overlapping epochs. Two technologists inspected the data independently using multiple bipolar and referential montages to isolate, and then remove, any data segments containing eye movement, muscle- or movement-related artifacts, or amplifier drift.

The power spectral frequency of the artifact-free EEG data was calculated using the BVA fast Fourier transform (FFT) function. The 512-point FFT was calculated for artifact-free 2-second epochs without windowing, with 0.5 Hz overlap at the limits of the band, and yielding a frequency resolution of 0.5 Hz. Absolute and relative power measures were calculated for each channel in four frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–20 Hz). EEG was obtained only at baseline and at the immediate intervention follow-up assessment.

Data analysis

Data were collected at four time points as noted earlier; however, for this feasibility study of the intervention and its effects on self-reported outcomes and neurocognitive tests, we report only on comparisons of pre-intervention to both immediate and four-month post-intervention measures. The latter comparison was selected because of our interest in the sustainability of post-intervention effects. We calculated means for PAOFI total, PAOFI memory, PAOFI HLC, BDI-II, STAI, and the 16 neurocognitive test scores at each of these time points. To assess for change over time, we conducted two separate ANOVAs to compare the scores from pre-intervention to immediate and four-month post-intervention. We also calculated the effect size (ES) at each post-intervention assessment. In addition, for the neurocognitive tests, a Reliability of Change Index (RCI) analysis was conducted, following the method of Jacobson and Truax (1991). We calculated RCIs for each neurocognitive measure to identify test score fluctuations that are both clinically and statistically meaningful, but it does not control for practice effect. As this was a feasibility study, we were interested in also exploring the reliability of our outcome measures to be used in a future RCT. The RCI procedure uses test–retest reliability data for each neurocognitive measure that allows for the derivation of standard error of measurement to calculate a 90 % reliable change confidence interval for the difference in performance between the two evaluations that is expected if no real change has occurred. A positive change on a measure falling outside the RCI range in 2 or more of the 16 neurocognitive outcomes was used as an indicator of meaningful improvement (Jenkins et al. 2006).

For the qEEG data, pre- to immediate post-intervention measures of global 'absolute power' (the total amount of power in a given frequency band) and 'relative power' (the amount of power in a given frequency band, relative to the total power across frequencies) were calculated for four frequency bands (delta, 0.5–4 Hz; theta, 4–8 Hz; alpha, 8–12 Hz; beta, 12–20 Hz). Pearson's r was used to examine associations between changes in EEG measures from pre-intervention to the immediate post-intervention time point, and changes in PAOFI scores from pre-intervention to the immediate post-intervention assessment time point. Additionally, EEG changes from pre- to immediate post-

intervention were examined in association with longer term changes in cognitive complaints as measured by the PAOFI changes at both the two-month and four-month post-intervention follow up assessments. PAOFI total, PAOFI memory, and PAOFI HLC scores were identified as a priori outcomes of interest based upon prior work (Ganz et al. 2013).

In parallel with correlational analyses, we identified high versus low improvers in the qEEG subsample by using a median split applied to change in PAOFI total score at immediate post-intervention, and generated topographic brain maps showing mean EEG changes in each frequency band for high and low improver groups. Maps were inspected for any visually salient between-group differences which were then followed up with an independent samples *t*-test.

Results

Sample characteristics

A total of 58 women inquired about the study and were screened for eligibility by telephone. Of these, 28 were not enrolled due to the following reasons: lack of sufficient memory complaints (n=7), too long since diagnosis (n=4), whole brain irradiation (n=1), depression (n=1), current marijuana user (n=1), history of ovarian cancer diagnosis (n=1), too busy to participate (n=7), refuse to participate before baseline (n=3), and scheduling conflicts (n=3). In all, 30 participants met criteria for the study, provided informed consent and were enrolled. Of the 30 enrolled participants, 3 dropped out after pre-intervention testing (family member became ill, lost to follow-up, and too busy to continue). Therefore, data from the 27 participants who completed the pre-intervention, immediate and four-month post-intervention assessments were analyzed for this report. There were no significant differences between those who dropped and those who completed the study on neurocognitive or self-report measures. They also did not significantly differ on any medical or demographic factors (data not shown, all p's >0.05).

Table 2 shows demographic and medical variables for all 27 participants, and the subset of 8 women who underwent qEEG. These eight participants were similar to the women who enrolled earlier and who were not part of the qEEG sub-study.

Evaluation of intervention outcomes

Self-reported cognitive complaints and mood We observed significant reductions in PAOFI total and memory subscale scores from pre-intervention to immediate post-intervention (t(26)=2.28, p=0.031; t(26)=2.81, p=0.009, respectively); these reductions were sustained at the four-month post-intervention assessment (t(26)=4.85, p<0.0001; t(26)=4.81. p<0.001, respectively). A significant reduction in HLC complaints was not seen until the four-month post-intervention (t(26)=3.08, p=0.005). Effect sizes for changes from pre- to immediate and to four-month post intervention, respectively, were as follows: PAOFI total: −0.479, −0.741; PAOFI memory: −0.517, −0.795; PAOFI HLC: −0.290, −0.638. No other changes reached significance. Scores on self-reported mood and anxiety measures did not change significantly over the intervention (data not shown). Therefore, we did not control for these variables in subsequent analyses of neurocognitive testing.

Neurocognitive tests ANOVA indicated short-term and long-term improvement on several measures. For instance, significant changes were found for Symbol Digit correct, Stroop Complex reaction time, Stroop reaction time correct, and Trails A time (df=26, all p's <0.05). Effect sizes for changes from pre- to immediate and to four-month post intervention, respectively, were as follows: Symbol digit: 0.429, 0.439; Stroop complex reaction time: 0.607, 0.741; Stroop reaction time: 0.324, 0.593; Trails A time: 0.488, 0.600. No other changes in cognitive tests reached significance.

The RCI analyses indicated that 5 of the 27 participants (19 %) showed meaningful improvement (i.e., change in 2 or more of 16 neurocognitive outcomes) from pre-intervention to the immediate post-intervention assessment, and 8 of the 27 (30 %) to the four-month post-intervention assessment (with 5 showing improvement on 3 or more measures). Reliable improvement was most often seen on measures of verbal learning and memory (Hopkins Verbal Learning Test-Revised) and processing speed (Symbol Digit) at immediate post-intervention; and, on processing speed (Symbol Digit) and divided attention (Shifting Attention Test) at four-month post-intervention.

qEEG and PAOFI outcomes

For the qEEG sub-study participants, mean pre-intervention PAOFI scores were 7.13 (SD=4.79) for PAOFI total, 2.63 (SD=1.93) for memory, and 1.88 (SD=2.10) for HLC. The strongest association between change in the EEG and PAOFI total was in the absolute alpha power measure, where the increase in alpha power was significantly associated with improvement in cognitive complaints at the two-month assessment (r=−0.815, p=0.014). Non-significant trend associations between PAOFI total and absolute alpha were observed at immediate post-intervention (r=−0.69, p=0.07), and four-month post-intervention (r=−0.608, p=0.110) time points. Change in alpha power at the immediate post-intervention time point correlated significantly with change in the PAOFI

Table 2 Demographic and medical characteristics of participants

Characteristic, % (n)	Total (N=27)	qEEG (n=8)	No qEEG (n=19)	p-value*
Age (mean ± SD)	54.1±6.3	54.3±4.7	54.0±6.9	0.9182
Race				
White	85 % (23)	88 % (7)	84 % (16)	0.9999
Non-White	15 % (4)	12 % (1)	16 % (3)	
Marital status				
Married	85 % (23)	88 % (7)	84 % (16)	0.9999
Not married	15 % (4)	12 % (1)	16 % (3)	
Education, years (mean ± SD)	16.4±1.9	17.3±2.0	16.1±1.8	0.1435
Employment status				
At least part-time	56 % (15)	50 % (4)	58 % (11)	0.9999
Unemployed	44 % (12)	50 % (4)	42 % (8)	
Household income				
≥$100,000	56 % (15)	75 % (6)	47 % (9)	0.2357
<$100,000	44 % (12)	25 % (2)	53 % (10)	
Years since diagnosis (mean ± SD)	2.8±1.0	2.5±0.5	2.9±1.1	0.2636
Surgery type				
Mastectomy	44 % (12)	38 % (3)	63 % (12)	0.3981
Lumpectomy	56 % (15)	62 % (5)	36 % (7)	
Chemotherapy				
Yes	89 % (24)	88 % (7)	89 % (17)	0.9999
No	11 % (3)	12 % (1)	11 % (2)	
Radiation				
Yes	63 % (17)	75 % (6)	58 % (11)	0.6655
No	36 % (10)	25 % (2)	42 % (8)	
Endocrine therapy				
Yes	67 % (18)	75 % (6)	63 % (12)	0.6758
No	33 % (9)	25 % (2)	37 % (7)	

*Chi-square or Fisher's exact tests for categorical variables and t-tests for continuous variables

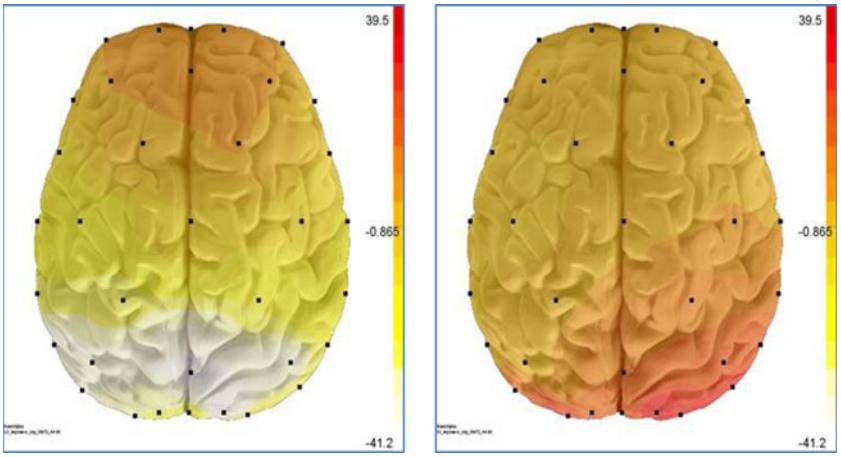
memory subscale at immediate post-intervention (r=−0.787, p=0.021) and at two-months (r=−0.878, p=0.004), and correlated significantly with change in the PAOFI HLC subscale at 2 months (r=−0.757, p=0.030) and at 4 months (r=−0.711, p=0.048).

Figure 1 shows topographic brain maps of the mean change in alpha power for participants who were classified at the immediate post-intervention time point as high improvers (mean change on PAOFI total=−4.25; SD=5.80) as compared to low improvers (PAOFI total change=1.00; SD=2.94) using a median split. Visual inspection suggested a group difference in the anterior –posterior (AP) gradient of alpha power where high improvers showed the more usual pattern of posterior alpha dominance. The group difference in AP gradient, calculated using values from anterior and posterior electrodes where AP gradient = *((anterior − posterior)/(anterior + posterior))*, approached significance (t(6)=2.35, p=0.057).

Discussion

We conducted the current study to determine the feasibility of a cognitive rehabilitation intervention program for BCS targeting improvement in cognitive complaints and objective cognitive test performance as potential outcomes. In addition, we explored the potential value of qEEG as a biomarker of brain neurophysiology that might track with the subjective assessments that were performed. Finally, we used the results of this pilot study to determine ES of the intervention and aid in the design of a future RCT to study the efficacy of the intervention. Regarding feasibility, the five-week program was well-received and well-tolerated based on participants' comments, their regular attendance, and the low attrition rate. Participants were able to engage in the intervention without undue frustration and discuss their experiences on the weekly homework assignments.

The outcomes that were assessed before and after the intervention allowed us to determine the range of intervention effects expected on various self-report and neurocognitive test outcomes. The ES were moderate to large, ranging from 0.33 to 0.61 for changes from pre- to immediate post-intervention; and from 0.44 to 0.74 from pre- to four-month post intervention. These results may over-estimate the ES given practice effects and the absence of a control group; however, these preliminary data were useful in the design of the phase II



Low Improvers (N = 4) High Improvers (N = 4)

Fig. 1 Changes in alpha power pre- vs. post-intervention for low and high improvers as determined by median split on changes in PAOFI total score. *Warm colors* represent higher activity. Visual inspection suggests that high improvers (*right*) generated more alpha globally, and generated the more usual pattern of posterior dominant alpha activity

randomized, controlled trial (RCT) of the intervention that is currently underway.

We also learned from the RCI that the memory and psychomotor/speeded attention and executive tests, in particular, have ample reliability to use in an RCT. Without a control group, we cannot rule out that improvement on these neurocognitive tests was related to practice effects from multiple administrations, but we are encouraged by observing significant reductions in self-reported cognitive problems overall, and specifically for memory, from pre-intervention to immediate follow-up. A reduction in HLC complaints, however, was not identified until the four-month follow-up, which raises the issue of possible self-perceptions of late effects or gains, versus natural resolution of problems versus practice effects. We anticipate that these questions will be resolved as part of the ongoing RCT.

On neurocognitive testing, the RCI analysis indicated that participants improved on at least two of 16 tests in the battery, and most often changes were on memory and tests of processing speed. Symbol Digit correct, Stroop complex reaction-time, Stroop reaction-correct and Trails A-time all improved at both immediate and four-month post-intervention. The two tests of attention set switching (CNS VS shifting attention-correct and Trails B-time) both had significant improvements at the four-month time point. These attention switching measures tests have strong executive components and appear to map on to the late effects of self-reported change in PAOFI HLC. This finding of later improvement on both self-reported and objective executive function will be an interesting phenomenon to examine in the RCT setting, as this may relate to improvement in perceived function as a result of practice or could reflect ongoing response

A. Example of a high difficulty Divided Attention exercise (Adapted from Rogers and Monsell, 1995)

Instructions: For each letter-number pair, alternate reporting whether the letter is a consonant or a volwel (Task 1) and whether the number is odd or even (Task 2).

L1 Con A8 Even E3 Vowel V9 Odd A6 ____ G6 _____ T12____

B. Example of a low difficulty level "Proof Reading" exercise (Adapted from Levine et al 2000).

Instructions: Read the paragraph. As you read, do the following:

1. **Circle words that are numbers (e.g. one, 7).**
2. **Underline words that are food (e.g. apples, meat).**
3. **Cross off words that are animals (e.g. ~~dog~~, ~~ant~~).**

Remember, if you get lost stop and ask yoursef "What am I doing?"

At the beginning, repeat the instructions, remind yourself what they are, and again, as you go along.

Two children went to the county fair. They pet ~~deer~~ and ~~ponies~~ at the petting zoo. They snacked on cotton candy and drank lemonade. They took two rides on the Tilt-a-Whirl, and stood in line 20 minutes for the haunted house ride. They worked up an appetite and ate corndogs while ~~pigeons~~ begged at their feet

Fig. 2 **A** Example of a high difficulty Divided Attention exercise (Adapted from Rogers and Monsell 1995). **B** Example of a low difficulty level "Proof Reading" exercise (adapted from Levine et al. 2000)

to the intervention program. These findings of delayed improvement also have implications for determining the length and intensity of cognitive training, and whether the amount or intensity of practice varies for specific target domains (i.e., to improve executive functions, attention, versus memory).

We found no significant pre- to post-intervention changes on mood or anxiety measures, but changes were in the direction of improvement. The lack of significant mood changes was not surprising since clinically depressed participants were excluded.

These pilot results from this intervention program compare favorably to others in the literature. Ferguson conducted a randomized comparison with a waitlist control group (Ferguson et al. 2007, 2012) in BCS to study a four-visit cognitive behavioral training intervention with telephone follow-ups to teach participants new coping strategies and to compensate for memory dysfunction. Significant post-intervention improvements were found in verbal memory and quality of life but not for cognitive complaints. Schuurs and Green (2012) conducted a non-randomized clinical trial of a 4-week cognitive intervention in 23 cancer survivors, compared to 9 waitlist control cancer survivors and to 23 adults who never had cancer. Compared to both comparison groups, the intervention group demonstrated improved memory and visuospatial function, subjective cognition, social functioning and less psychosocial distress. Cognitive gains were maintained over 3 months. In a three-to-five week inpatient rehabilitation protocol for female breast cancer patients immediately following acute cancer treatment, Poppelreuter and colleagues (2009) found that most scores on a neuropsychological battery improved after both computer and traditional cognitive training, but the improvement was not more than that found after patients attended the usual inpatient rehabilitation program. Von Ah and colleagues (2012) administered computer based processing speed or memory training compared to a waitlist control condition. Processing speed training improved processing speed and immediate memory immediately and 2 months after the intervention; memory training improved memory at the two-month follow-up. The results of these and the current report share the common finding that cancer survivors may show improvements on objective and/or subjective measures, and that some improvements may be delayed with practice of intervention strategies. No specific intervention stands out as superior to another. Larger, controlled clinical trials are needed.

The qEEG results suggest that the cognitive improvements seen with this intervention in BCS are reflected in measurable changes in brain function. We observed a linear relationship between increased global alpha power over the five-week intervention and decreased cognitive complaints across post-intervention visits. Although our qEEG analyses were exploratory and small in sample size, it is notable that alpha power has previously been linked to level of cognitive function (Bucci et al. 2007; Hogan et al. 2003). In a study of the neurotoxic effects of chemotherapy in BCS, asymmetry of the alpha rhythm of ≥0.5 Hz was found in 7 of 17 patients who were treated with high doses of chemotherapy and in 2 of 16 patients who underwent standard doses of chemotherapy (Schagen et al. 2001). Future studies should examine alpha power as a prospectively identified measure of interest and attempt to replicate this finding in independent samples.

The major limitation of this study is lack of a comparison control group that would account for practice effects on neurocognitive testing, as well as subjective reports of improvement unrelated to the content of the intervention program. However, without some preliminary support of benefit of the intervention program, it would have been difficult to justify moving to a larger scale RCT. While alternate forms were used on several measures to reduce the effects of practice on outcomes, the RCI method used did not control for practice effects but rather it only indicates whether a given participant's score falls outside the 90 % confidence interval surrounding their baseline score. As the focus of this study was on the feasibility of delivering the intervention (versus determining the degree to which the intervention changed self-reported or cognitive outcomes), we were aware that making conclusive statements about individual change and treatment efficacy would be difficult.

In conclusion, the results of this study are promising: participants engaged in and tolerated the intervention well, demonstrated improvement in cognitive complaints and on neurocognitive tests that were sustained, and showed changes in brain function that were associated with this improvement. This preliminary evidence of efficacy as well as physiologic changes in brain function serve as the basis for a RCT to more rigorously evaluate treatment efficacy.

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Appendix: Details of cognitive training protocol

The cognitive rehabilitation intervention is a 5-week, 2-hour-per-session intervention.

Attention Because attention dysfunction is a major complaint associated with "chemo brain" and often has downstream effects on other cognitive functions, the first two weeks emphasized attention enhancing strategies. Attention exercises targeted vigilance, concentration, selective attention, alternating/switching attention and working memory (White and Shah 2006; Wilson 2003). Week 1 focused

on vigilance and expanding concentration. These exercises involved visual searches for numbers in an array, and listening for target letters in an array. To improve concentration, participants first found their 'baseline' attention span by performing an attention exercise and using a stopwatch to note how much time passed before they felt their attention wane (e.g. 60 s). Participants would then work on the exercise again, but stop before their baseline (e.g. stop after 45 s), and repeat this process, gradually extending the time they worked without feeling distracted, until they surpassed their baseline (e.g. from 45 to 50 s, then 60, then 75 s etc.). For reducing distractibility, participants were instructed to first perform exercises in a quiet room, and then with mastery, perform exercises under increasingly distracting conditions (e.g. with the radio or TV on, in a public place). Week 2 focused on more complex attentional functions, including divided attention, selective attention, and alternating attention. For example, participants performed exercises that required them to perform mental operations that alternated between focusing on numbers and letters; to sequence numbers and letters in forward and reverse order; and, to ignore irrelevant stimuli. Figure 2A provides an example of an alternating attention exercise (Rogers and Monsell 1995). Participants were told that improving attention would take time and were encourage to practice the exercises over the 5-week course.

Executive function These exercises involved plan development and execution, organizing, goal management, using checklists, word generation grids and multi-tasking. Examples of class exercises for executive function included using a check list and organizational strategies for following a recipe (e.g. check for ingredients, lay out wet and dry ingredients and utensils, preheat oven, etc.), and for organizing a pot-luck (e.g. budgeting, planning meals around food preferences of guests, assigning food to bring). Executive exercises also focused on working memory and dual-task performance. Figure 2B is an example of a dual-task 'proof reading' exercise (Levine et al. 2000).

Memory Participants learned mnemonic strategies involving association, imagery, story creation, and semantic organization (McCarty 1980; Verhaeghen et al. 1992; Yesavage 1985). Exercises included using these mnemonic strategies for remembering daily life information such as street names, names of books and authors, faces and names, and for shopping. Effective use of practical memory strategies (e.g. post-it notes, calendars) was also discussed. They also were told to use these memory strategies in daily life, as in when grocery shopping.

Education Participants received education about memory, attention and executive functions, and empirical studies of the effects of chemotherapy on cognition. This was done in session 1 and at the beginning of each week that related to the specific topic to be discussed. Education provided a foundation for understanding their own strengths and weaknesses and for understanding how and why their exercises were targeting the relevant cognitive functions. To cope with anxiety that may be related to engaging in homework exercises, participants received training in deep breathing, muscle relaxation, countering negative thoughts, self-pacing, taking breaks, and spacing practice (Stigsdotter 2000)

Goal setting Participants formulated their own concrete, measurable short- and long-term goals. Short-term goal (e.g. "organizing my closet for 15 min") attainment was reviewed weekly, and new goals were set as prior goals were met. Participants finalized a long-term goal (e.g. "plan a birthday party") by the last session and attainment of that goal was assessed by the study coordinator at the follow-up visits. We explained to participants that an important part of accomplishing a goal was to schedule it with themselves, as if it were an appointment. Hence, if a participant needed to buy and send a greeting card, they would estimate how much time this would take (e.g. 30 min), use a calendar to determine when they could fit this in (e.g. 20 min go to the store on Saturday at 10 am; 10 min to write a message in the card Sunday at 10 am). We educated participants that long-term goals were actually a series of short-term goals that could be met in stages to accomplish the larger goal. For instance, planning a child's birthday party would involve setting the date for the party, estimating how many to invite, and setting up smaller goals to write invitations, call venues to reserve an activity or cake etc.

References

Ahles, T. A., & Saykin, A. J. (2007). Candidate mechanisms for chemotherapy-induced cognitive changes. *Nature Reviews. Cancer, 7*(3), 192–201.

Ahles, T. A., Saykin, A. J., Furstenberg, C. T., Cole, B., Mott, L. A., Skalla, K., et al. (2002). Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *Journal of Clinical Oncology, 20*(2), 485–493.

Ahles, T. A., Saykin, A. J., McDonald, B. C., Li, Y., Furstenberg, C. T., Hanscom, B. S., et al. (2010). Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. *Journal of Clinical Oncology.* doi:10.1200/JCO.2009.27.0827.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory-II*. San Antonio: Psychological Corporation.

Benedict, R. H. (1997). *Brief Visuospatial Memory Test-Revised professional manual*. Odessa, FL: Psychological Assessment Resources, Inc.

Benton, A. L., Sivan, A. B., Hamsher, K. deS., Varney, N. R., Spreen, O. (1994). *Contributions to neuropsychological assessment*. A clinical manual (2nd ed.). New York: Oxford University Press.

Boykoff, N., Moieni, M., & Subramanian, S. (2009). Confronting chemobrain: an in-depth look at survivors' reports of impact on work, social networks, and health care response. *Journal of Cancer Survivorship, 3*(4), 223–232.

Brandt, J., & Benedict, R. H. B. (2001). *Hopkins Verbal Learning Test —Revised. Professional manual*. Lutz, FL: Psychological Assessment Resources, Inc.

Bucci, P., Galderisi, S., Catapano, F., Di Benedetto, R., Piegari, G., Mucci, A., et al. (2007). Neurocognitive indices of executive hypercontrol in obsessive-compulsive disorder. *Acta Psychiatrica Scandinavica, 115*(5), 380–387.

Burnam, A. M., Wells, K. B., Leake, B., & Landsverk, J. (1988). Development of a brief screening instrument for detecting depressive disorders. *Medical Care, 26*(8), 775–789.

Castellon, S. A., Ganz, P. A., Bower, J. E., Petersen, L. A., Abraham, L., & Greendale, G. A. (2004). Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. *Journal of Clinical and Experimental Neuropsychology, 26*(7), 955–969.

Cavallini, E., Pagnin, A., & Vecchi, T. (2003). Aging and everyday memory: the beneficial effect of memory training. *Archives of Gerontology and Geriatrics, 37*(3), 241–257.

Cavallini, E., Dunlosky, J., Bottiroli, S., Hertzog, C., & Vecchi, T. (2010). Promoting transfer in memory training for older adults. *Aging Clinical and Experimental Research, 22*(4), 314–323.

Chelune, G. J., Heaton, R. K., & Lehman, R. A. W. (1986). Neuropsychological and personality correlates of patients' complaints of disability. In R. E. Tarter & G. Goldstein (Eds.), *Advances in clinical neuropsychology* (Vol. 3, pp. 95–126). New York: Plenum Press.

Cull, A., Hay, C., Love, S. B., Mackie, M., Smets, E., & Stewart, M. (1996). What do cancer patients mean when they complain of concentration and memory problems? *British Journal of Cancer, 74*(10), 1674–1679.

Ferguson, R. J., & Ahles, T. A. (2003). Low neuropsychologic performance among adult cancer survivors treated with chemotherapy. *Current Neurology and Neuroscience Reports, 3*(3), 215–222.

Ferguson, R. J., Ahles, T. A., Saykin, A. J., McDonald, B. C., Furstenberg, C. T., Cole, B. F., et al. (2007). Cognitive-behavioral management of chemotherapy-related cognitive change. *Psycho-Oncology, 16*(8), 772–777.

Ferguson, R. J., McDonald, B. C., Rocque, M. A., Furstenberg, C. T., Horrigan, S., Ahles, T. A., et al. (2012). Development of CBT for chemotherapy-related cognitive change: results of a waitlist control trial. *Psycho-Oncology, 21*(2), 176–186.

Ganz, P. A., Kwan, L., Castellon, S. A., Oppenheim, A., Bower, J. E., Silverman, D. H. S., et al. (2013). Cognitive complaints after breast cancer treatments: examining the relationship with neuropsychological test performance. *Journal of the National Cancer Institute*. doi:10.1093/jnci/djt073.

Gronwall, D. M. A. (1977). Paced auditory serial-addition task: A measure of recovery from concussion. *Perceptual and Motor Skills, 44*, 367–373.

Gualtieri, C. T. Johnson, L. G. (2006). Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. *Archives of Clinical Neuropsychology, 21*(7), 623–643.

Hogan, M. J., Swanwick, G. R., Kaiser, J., Rowan, M., & Lawlor, B. (2003). Memory-related EEG power and coherence reductions in mild Alzheimer's disease. *International Journal of Psychophysiology, 49*(2), 147–163.

Hurria, A., Somlo, G., & Ahles, T. (2007). Renaming chemobrain. *Cancer Investigation, 25*(6), 373–377.

Jacobson, N. S., & Truax, P. (1991). Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology, 59*(1), 12–19.

Janelsins, M. C., Kohli, S., Mohile, S. G., Usuki, K., Ahles, T. A., & Morrow, G. R. (2011). An update on cancer- and chemotherapy-related cognitive dysfunction: current status. *Seminars in Oncology, 38*(3), 431–438.

Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., & Thun, M. J. (2009). Cancer statistics, 2009. *CA: A Cancer Journal for Clinicians, 59*(4), 225–249.

Jenkins, V., Shilling, V., Deutsch, G., Bloomfield, D., Morris, R., Allan, S., et al. (2006). A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. *British Journal of Cancer, 94*(6), 828–834.

Jim, H. S., Phillips, K. M., Chait, S., Faul, L. A., Popa, M. A., Lee, Y. H., et al. (2012). Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *Journal of Clinical Oncology, 30*(29), 3578–3587.

Levine, B., Robertson, I. H., Clare, L., Carter, G., Hong, J., Wilson, B. A., et al. (2000). Rehabilitation of executive functioning: an experimental-clinical validation of Goal Management Training. *Journal of International Neuropsychological Society, 6*(3), 299–312.

Lustig, C., Shah, P., Seidler, R., & Reuter-Lorenz, P. (2009). Aging, training, and the brain: a review and future directions. *Neuropsychology Review, 19*(4), 504–522.

McCarty, D. L. (1980). Investigation of a visual imagery mnemonic device for acquiring face–name associations. *Journal of Experimental Psychology: Human Learning and Memory, 6*(2), 145–155.

Moore Sohlberg, M., & Mateer, C. A. (2001). *Cognitive rehabilitation: An integrative neuropsychological approach*. New York: Guilford Press.

O'Brien, A. R., Chiaravalloti, N., Goverover, Y., & DeLuca, J. (2008). Evidenced-based cognitive rehabilitation for persons with multiple sclerosis: a review of the literature. *Archives of Physical Medicine and Rehabilitation, 89*(4), 761–769.

Poppelreuter, M., Weis, J., & Bartsch, H. H. (2009). Effects of specific neuropsychological training programs for breast cancer patients after adjuvant chemotherapy. *Journal of Psychosocial Oncology, 27*(2), 274–296.

Reid-Arndt, S. A., Yee, A., Perry, M. C., & Hsieh, C. (2009). Cognitive and psychological factors associated with early posttreatment functional outcomes in breast cancer survivors. *Journal of Psychosocial Oncology, 27*(4), 415–434.

Rogers, R. D., & Monsell, S. (1995). Costs of a predictable switch between simple cognitive tasks. *Journal of Experimental Psychology:General, 124*, 207–231.

Schagen, S. B., Hamburger, H. L., Muller, M. J., Boogerd, W., & van Dam, F. S. (2001). Neurophysiological evaluation of late effects of adjuvant high-dose chemotherapy on cognitive function. *Journal of Neuro-Oncology, 51*(2), 159–165.

Schagen, S. B., Muller, M. J., Boogerd, W., Rosenbrand, R. M., van Rhijn, D., Rodenhuis, S., et al. (2002). Late effects of adjuvant chemotherapy on cognitive function: a follow-up study in breast cancer patients. *Annals of Oncology, 13*(9), 1387–1397.

Schagen, S. B., Vardy, J., & Steering Committee of the International Cognition and Cancer Task Force. (2007). Cognitive dysfunction in people with cancer. *The Lancet Oncology, 8*(10), 852–853.

Schilder, C. M., Seynaeve, C., Beex, L. V., Boogerd, W., Linn, S. C., Gundy, C. M., et al. (2010). Effects of tamoxifen and exemestane on cognitive functioning of postmenopausal patients with breast cancer: results from the neuropsychological side study of the tamoxifen and exemestane adjuvant multinational trial. *Journal of Clinical Oncology, 28*(8), 1294–1300.

Schuurs, A., & Green, H. J. (2012). A feasibility study of group cognitive rehabilitation for cancer survivors: enhancing cognitive function and quality of life. *Psycho-Oncology*. doi:10.1002/pon.3102.

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. G. (1971). *Manual for the State-Trait Anxiety Inventory*. Palo Alto: Consulting Press.

Spreen, O., & Strauss, E. (1998). *A compendium of neuropsychological tests* (2nd ed.). New York: Oxford University Press.

Stigsdotter, N. A. (2000). Multifactorial memory training in normal aging: In search of memory improvement beyond the ordinary. In

R. Hill, L. Backman, & N. A. Stigsdotter (Eds.), *Cognitive rehabilitation in old age*. New York: Oxford University Press.

Tannock, I. F., Ahles, T. A., Ganz, P. A., & van Dam, F. S. (2004). Cognitive impairment associated with chemotherapy for cancer: report of a workshop. *Journal of Clinical Oncology, 22*(11), 2233–2239.

Turner, G., & Levine, B. (2004). Disorders of executive function and self-awareness. In J. Ponsford (Ed.), *Rehabilitation of neurobehavioral disorders*. New York: Guilford Press.

Vardy, J., Rourke, S., & Tannock, I. F. (2007). Evaluation of cognitive function associated with chemotherapy: a review of published studies and recommendations for future research. *Journal of Clinical Oncology, 25*(17), 2455–2463.

Vardy, J., Wefel, J. S., Ahles, T., Tannock, I. F., & Schagen, S. B. (2008). Cancer and cancer-therapy related cognitive dysfunction: an international perspective from the Venice cognitive workshop. *Annals of Oncology, 19*(4), 623–629.

Verhaeghen, P., Marcoen, A., & Goossens, L. (1992). Improving memory performance in the aged through mnemonic training: a meta-analytic study. *Psychology and Aging, 7*(2), 242–251.

Von Ah, D., Carpenter, J.S., Saykin, A., Monahan, P., Wu, J., Yu, M., Rebok, G., Ball, K., Schneider, B., Weaver, M., Tallman, E., & Unverzagt, F. (2012). Breast Cancer Research and Treatment 135 (3), 799–809.

Wefel, J. S., & Schagen, S. B. (2012). Chemotherapy-related cognitive dysfunction. *Current Neurology and Neuroscience Reports, 12* (3), 267–275.

Wefel, J. S., Lenzi, R., Theriault, R. L., Davis, R. N., & Meyers, C. A. (2004). The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. *Cancer, 100* (11), 2292–2299.

White, H. A., & Shah, P. (2006). Training attention-switching ability in adults with ADHD. *Journal of Attention Disorders, 10*(1), 44–53.

Wilson, B. (2003). *Neuropsychological rehabilitation: Theory and practice*. New York: Psychology Press.

Yesavage, J. A. (1985). Nonpharmacologic treatments for memory losses with normal aging. *The American Journal of Psychiatry, 142*(5), 600–605.