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PROJECT ABSTRACT

For millions of cancer survivors, cognitive impairment is a prevalent, severe, and persistent problem that is associated with other symptoms (depressive symptoms, anxiety and fatigue), poorer work ability, and poorer quality of life. Available evidence, including work by our own group, suggests that cognitive training may be a viable treatment option. However, to date, these studies are limited as none have been conducted in the home and therefore fail to address the transferability of these empirically based cognitive training programs to general practice.

The purpose of this translational research is to conduct a home based single-blind, randomized controlled trial to test the feasibility, satisfaction, and preliminary efficacy of cognitive training compared to attention control in breast cancer survivors (BCS) as well as to explore potential biomarkers of intervention effects.

Specific aims are to: (1) examine the feasibility (facilitators and barriers) and satisfaction of the computer-based cognitive training program; (2) test the preliminary efficacy of cognitive training on improving cognitive performance (memory, processing speed, attention, working memory, executive function) over time compared to attention control; (3) evaluate cognitive training effects on associated outcomes compared to attention control; and (4) explore the effect of computerized cognitive training on serum brain derived neurotrophic factor (BDNF) over time compared to attention control. BDNF is widely distributed in the brain, plays a crucial role in neuroplasticity and has been observed to correlate with cognitive function in cancer patients. A total of 68 eligible BCS will be randomized to computerized cognitive training or attention control. A blinded and trained tester will perform data collection and neuropsychological testing at two time points: baseline prior to intervention (T1) and immediately after the 10-week cognitive training -program (within 90 days) (T2). Feasibility and satisfaction will be assessed through objective indicators (study adherence, completion rate) and self-report (facilitators, barriers, and perceived satisfaction) and cognitive performance will be assessed through objective neuropsychological tests of memory, processing speed, attention, working memory, executive function assessed over the phone. In addition, we will measure the effects of cognitive training on self-report measures of perceived cognitive function, associated symptoms (depressive symptoms, anxiety and fatigue), perceived work ability, and quality of life. Data will be analyzed using descriptive statistics and a general linear mixed model (GLMM). Simple main effects analyses will be used to follow up statistically significant interactions.

This research innovatively builds on our previous research by: 1) translating findings from the laboratory to the home setting and importantly seeks to identify facilitators and barriers of intervention use; 2) addresses limitations of previous trials (uses an attention control rather than a no-contact or wait-list control), (3) examines cognitive training effects on real-life outcomes such as associated symptoms, perceived work ability and quality of life; and (4) will be the first study in cancer survivors to explore levels of BDNF as a potentially sensitive outcome measure of intervention effects over time compared to attention control. Findings from this study will provide necessary information about the feasibility, satisfaction and preliminary efficacy of the home-based cognitive training on memory performance and processing speed as well as its effects on associated outcomes in BCS. Positive results will lead to a larger, full-scale study to determine efficacy and build evidence-based treatment for clinicians to use in treating BCS with cognitive impairment.

1. SPECIFIC AIMS

The goal of this translational research study is to determine the feasibility, satisfaction and preliminary efficacy of cognitive training delivered in the home for cancer survivors suffering from cancer- and cancer-treatment-related cognitive impairment. In addition, this will be the first study in cancer to explore levels of brain derived neurotrophic factor (BDNF), which we now know is associated with neural plasticity, as a potentially sensitive outcome measure of intervention effects over time compared to attention control.

Cancer- and cancer-treatment-related cognitive impairment is a national research priority.1 Up to 75% of the 2.6 million breast cancer survivors (BCS) living in the United States2-4 report problems with memory or feelings of mental slowness.4,5 Deficits in memory and processing speed have also been documented on neuropsychological exam6-13 and functional magnetic resonance imaging (fMRI).14-18 Cognitive impairment is a prevalent, severe, and persistent problem that is associated with other symptoms (depressive symptoms, anxiety symptoms, fatigue), poorer work ability19-28 and poorer quality of life.19,29-34 Cognitive training may be a viable treatment option.35 To date, a total of 8 pilot studies, including our own randomized controlled trial36 have noted positive effects of cognitive training in cancer survivors.34,36-42 These findings, combined with evidence from studies in the well elderly,43,44 suggest that cognitive training interventions to promote neuroplasticity are likely to be beneficial; however, these studies are limited as most have been conducted in the home and therefore, fail to address the transferability of these cognitive training programs to general practice. **Therefore, the purpose of this translational research** is to conduct a home based single-blind, randomized controlled trial to test the feasibility, satisfaction, and preliminary efficacy of cognitive training delivered in the home setting compared to attention control in breast cancer survivors (BCS). In addition, this will be the first study in cancer to explore levels of brain derived neurotrophic factor (BDNF).

Specific aims are to: (1) examine the feasibility (facilitators and barriers to use) and satisfaction of the computerized cognitive training program; (2) test the preliminary efficacy of cognitive training on improving objective cognitive performance over time compared to attention control; (3) evaluate cognitive training effects on associated outcomes over time compared to attention control and (4) explore the effect of computerized cognitive training on serum brain derived neurotrophic factor (BDNF) over time compared to attention control. A total of 68 eligible BCS will be randomized to cognitive training or attention control. A blinded and trained tester will perform data collection and neuropsychological testing at two time points: baseline prior to intervention (T1) and immediately after the 10-week cognitive training program (within 90 days) (T2). Feasibility and satisfaction will be assessed through objective indicators (study adherence, completion rate) and self-report and memory and speed of processing will be assessed through objective neuropsychological tests. In addition, we will measure the effects of cognitive training on self-report measures of perceived cognitive function, associated symptoms (depressive symptoms, anxiety and fatigue), perceived work ability, and quality of life**.**

Innovatively, the proposed study builds on our pilot results and addresses limitations of previous trials including: (1) uses home based training; (2) uses an attention control rather than a no-contact or wait-list control; (3) uses optimal intervention dose based on evidence, (4) explores cognitive training effects on real-life outcomes such as perceived cognitive impairment (using new PROMIS measures), associate symptoms, perceived work ability, and quality of life. This will also be the first study in the context of cancer to examine BDNF as a biomarker of intervention effects.

1.1 Specific Aims and Hypotheses are:

Aim 1: To evaluate the feasibility (including facilitators and barriers to use) and satisfaction of computerized cognitive training delivered in the home among BCS.

Hypothesis 1: BCS assigned to the cognitive training arm will perceive the intervention as more acceptable and useful than BCS assigned to the attention control condition.

Aim 2: To test the preliminary efficacy of the cognitive training intervention for improving perceived cognitive function over time compared to attention control.

Hypothesis 2.1: The intervention group will have greater improvement in subjectively measured cognitive function (Perceived cognitive impairment and Perceived cognitive capabilities) over time compared to attention control.

Secondary and exploratory aims
Aim 3: To evaluate computerized cognitive training effects on secondary outcomes over time compared to attention control.

Hypothesis 3: The intervention group will demonstrate greater improvement in work ability, health perceptions, and quality of life over time compared to attention control.

Aim 4: To test the preliminary efficacy of the cognitive training intervention for improving objective cognitive performance over time compared to attention control.

Hypothesis: 4: The intervention group will have greater improvement in objectively measured cognitive function over time compared to attention control.

Aim 5 (exploratory): Explore the effect of computerized cognitive training on serum BDNF levels over time compared to attention control.

2. SIGNIFICANCE

Research on cognitive impairment in cancer is a national priority: The President's Cancer Panel,[1] the Institute of Medicine Executive Summary, the National Cancer Institute Office of Cancer Survivorship[45] and the National Institute of Nursing Research Strategic Plan[46] have all identified management of symptoms including cognitive impairment, as a top research priority. **Research on breast cancer survivors (BCS) is vitally important:** This research focuses on BCS, the largest group of female cancer survivors. Breast cancer is the second most common cancer among women, with one out of eight women, or approximately 12.4% of American women being diagnosed with breast cancer at some time in their life.[47] In 2015, more than 230,000 women were diagnosed with breast cancer in the U.S. alone[48] with five-year relative survival rates at 98% for local stage tumors. Because BCS constitute the largest group in the cancer survivor community, management of symptoms experienced by these women, such as cognitive impairment is vitally important.[1] **Cognitive impairment is a prevalent, severe, and persistent problem for BCS**: Up to 75%[4,49] of BCS report some level of cognitive impairment.[4,6-9,50-52] Meta-analyses of studies of cancer survivors, including BCS, have documented that cognitive dysfunction can be both severe and a life-changing symptom.[6-8,10-13] The largest meta-analysis with 30 studies showed moderate to large decrements in memory (*d* = -0.61 to -0.91) and speed of processing (*d* = -0.70) in adult cancer survivors compared to controls.[10] Similarly, a recent meta-analysis of 27 studies of BCS (over 1,562 subjects) found small to moderate decrements not only in memory and processing speed; but, also in attention, working memory and executive function in both cross-sectional and longitudinal studies.[11] Although longitudinal studies have identified cognitive dysfunction after surgery and prior to

chemotherapy and during the acute phase of treatment (e.g. during chemotherapy),[53] BCS report that cognitive dysfunction is most disruptive and bothersome after treatment (≥6 months post-treatment), when other cancer treatment-related symptoms have subsided, and they face returning to work.[53-56]

A growing body of research including our own studies has shown that a substantial number of BCS continue to have objectively measured memory deficits for up to 20 years post-treatment[49,57-5960] and that BCS perceive cognitive impairment as disruptive and bothersome.[54,61] **Cognitive impairment is associated with other symptoms (depressive symptoms, anxiety and fatigue), poor perceived work ability, and poorer quality of life:** Perceived cognitive impairment consistently correlates with higher levels of depressive symptoms, anxiety, and fatigue.[54,62] In fact, these symptoms have been shown to be the most common symptoms reported post-primary treatment. [45] In addition, multiple studies have also shown that cognitive impairment demonstrated on neuropsychological tests is associated with higher levels of depressive symptoms, fatigue, and anxiety.[29,58,63-66] In our own study of 444 BCS compared to 355 healthy women, cancer- and cancer-treatment related cognitive impairment on neuropsychological tests was significantly related to depressive symptoms and fatigue.[67] Furthermore, surveys and qualitative studies by our team and others indicate that cognitive impairment can dramatically affect perceived work ability[19-28] and quality of life.[29,33,57,68-71]

There is an urgent need to build the evidence base for treatment of cognitive impairment in cancer survivors. Computerized cognitive training may be a viable treatment option.[35] To date, a total of 8 pilot studies, including our own randomized controlled trial,[36] have noted positive effects of computerized cognitive training in cancer survivors.[34,36-42] These findings suggest that computerized cognitive training interventions are likely to be beneficial; however, these studies are limited as they fail to address feasibility issues for implementing a home based intervention

3. INNOVATION

This will be one of the first studies to deliver a computerized cognitive training program to cancer survivors in the home. Delivery of the home based computerized cognitive training has several advantages, including: (1) mitigates transportation needs and thereby, improves participation/access to those who would otherwise been unable to (e.g. rural BCS); (2) alleviates scheduling difficulties; (3) reduces expenses especially when compared to nurse-led, supervised programs;[72] and (4) ultimately, allows BCS a role in self-management of this symptom. [73] **This will be the first trial to leverage an existing and readily available computerized cognitive training program in cancer survivors**. Brain HQ (formerly InSight), utilized in our university-based, RWJF-pilot has never been fully tested in a representative population of BCS in their home. Using the readily available Brain HQ program would leverage the significant investment made to originally develop these resources and may expand its usefulness in translating to the large population of BCS. **Fully testing this program has many important advantages for clinical practice and public health including:** (1) the program addresses deficits in memory, speed of processing, and executive function which have been linked to diminished life quality and poor perceived work ability, both of which have functional and economic impact for BCSs and their families; (2) the program is readily available and, if determined efficacious, its uptake could be immediate and cost-effective; (3) the program adjusts for individual performance and thus would support BCS with varying deficit levels; and (4) the program is practical and relatively easy to use and therefore would allow BCS a role in self-management of this symptom. [73]

This will be the first randomized, controlled trial of computerized cognitive training to adequately address placebo effects. Previous studies in cancer survivors are limited by the use of a no-contact or wait-list control comparison group, a study approach that fails to fully

address potential placebo effects. In this enhanced proposal, we will use an attention control comparison group that will reduce the variability of factors and biases that might influence outcomes of the trial. According to the Center for Drug Evaluation and Treatment[74] and others,[75,76] a well-designed control condition is an essential component of behavioral intervention trials. Employing an attention control comparison group like the one proposed in this study that is similar to the intervention, but does not have the active component to modify cognitive function, will enhance the study by (1) providing a more suitable alternative and, consequently, enhance recruitment and retention of participants; (2) improve the internal validity of the study; and (3) ensure that the "true effects of the intervention can be discerned."[75]

This will be the first randomized, controlled trial to explore the impact of computerized cognitive training on tangible, real-life outcomes, such as perceived work ability in cancer survivors and BCS. Considerable research suggests that cognitive impairment after cancer and cancer treatment negatively impacts perceived work ability in cancer survivors.[19-28] Theoretical models suggest a crucial link between cognitive impairment and work-related outcomes in cancer survivors.[77-79] To understand this link better, our team completed a comprehensive review of the literature and found a total of 20 empirical studies (9 qualitative, 10 quantitative and 1 mixed-methods) that demonstrated the deleterious effects of perceived cognitive impairment on work-related outcomes including perceived work ability.[19-28,30,31,61,80-85] Based on our work and that of others, it is imperative that we explore the impact of cognitive training programs on the real-world issues of work ability in BCS.

This is the first study in cancer to examine BDNF as a potentially sensitive outcome measure that will increase our ability to measure intervention efficacy. Brain derived neurotrophic factor (BDNF) is a neurotropin that is widely distributed in the brain and plays a crucial role in neurodevelopment, neuronal function, and neuroplasticity.[86-88] Pre-clinical studies in animals have noted that spatial memory is impaired when BDNF signaling is decreased;[89,90] alternatively, brain BDNF was shown to be increased during a spatial learning task[89] and when rodents are housed in cognitively stimulating environments.[91] In clinical studies, including our own pilot, researchers have noted that serum BDNF levels were significantly increased after computerized cognitive training in non-cancer populations.[92,93] In cancer, one small study showed that BDNF levels were associated with correct responses on cognitive tests; suggesting that serum BDNF levels may be a sensitive measure of cognitive function.[94] However, there have been no studies examining serum BDNF levels as an outcome measure of computerized cognitive training efficacy in cancer. Identifying a sensitive biomarker of neuroplasticity will aid future efficacy and effectiveness trials and ultimately, help guide the development of evidence-based treatment guidelines.

4. APPROACH

PRELIMINARY STUDIES: The proposed study will leverage the expertise of an interdisciplinary team of experts in cancer, neuro-psychological assessment, statistics and cognitive training in BCS). Our team has been internally (ACS) and externally funded (RWJF and Walther Cancer Institute) and have conducted multiple studies which have (1) documented clinically significant memory impairment in 52 BCS compared to age and education matched healthy control women;[59] (2) examined the impact of perceived cognitive impairment in 134 BCS and found that those with more cognitive concerns had poorer QOL, including more depressive symptoms, lower well-being, poorer physical functioning, and greater fatigue;[33] (3) interviewed 22 BCS which revealed that BCS incur cognitive concerns including memory and processing speed and that those deficits impact their self-esteem, social relationships, and work ability;[19] and most recently (4) we completed the **Advanced Cognitive Training in Breast Cancer Survivors (PI: Von Ah).** With funding from the Robert Wood Johnson Foundation, we conducted a randomized controlled trial comparing two cognitive training interventions (memory and computerized cognitive training) to a wait-list control group in 82 female BCS at the IUSON.

Computerized cognitive training (InSight) compared to wait-list control, resulted in immediate and durable improvements in neuropsychological measures of (1) memory at post-intervention and 2-month follow-up (effect sizes=0.75 and 0.82; respectively; p<.01) and (2) processing speed at post-intervention and 2-month follow-up (effect sizes=0.55 and 0.67, p<0.05). InSight training also had the advantage of demonstrating improved perceived cognitive functioning, associated symptoms (less depressive symptoms, anxiety and fatigue), and quality of life.[36] **This important work represents one of the largest RCT in computerized cognitive training in BCS to date and the only one to include a neuropsychological battery. The next logical step is to build on this previous work and translate the findings to general practice.**

5. STUDY DESIGN

The proposed design is a two-group, randomized, controlled trial. After providing consent and completing a baseline assessment, a total of 68 eligible BCS will be randomized to computerized cognitive training or computerized attention control. Training sessions have been standardized across the BrainHQ training and attention control groups with each group completing up to 40 hours over 10 week period (total of up to 40 hours), with the dose based on previous research.[36] Outcomes will be assessed at baseline and immediately post-intervention (within 90 days).

6. ELIGIBILITY CRITERIA

6.1 Inclusion criteria

1. Female gender
2. ≥ 21 years old at the time of informed consent
3. Ability to provide written informed consent and HIPAA authorization
4. First diagnosis of non-metastatic breast cancer.
5. Self-reported cognitive impairment
6. Subjects seeking treatment though not currently being treated or with prior treatment history for cognitive impairment.
7. ≥ 1 year post-treatment including surgery, radiation, and/or chemotherapy
8. Ability to understand, speak, read, and write English

6.2 Exclusion criteria

1. Comorbidities that would sufficiently impair performance or inhibit cognitive training such as: history of stroke, encephalitis, traumatic brain injury, brain surgery, dementia, or Alzheimers disease.
2. Cranial radiation or intrathecal therapy.
3. Current active major depression or substance abuse or history of bipolar disorder psychosis, schizophrenia, or learning disability.
4. History of current or other cancer except for basal cell skin cancer.

No potential participant will be excluded due to not having a computer. The study will provide a computer tablet with data capability to ensure access to participate. This need is not estimated to be high as the most recent Census data identified that 84% of U.S. households own a computer and 73% have a computer with a broadband connection to the internet.

7. PATIENT REGISTRATION

All patients will be registered with the Indiana University School of Nursing. Regulatory files will be maintained by the Indiana University School of Nursing Research Department for Breast Cancer Survivorship. Applicable regulatory documents must be completed and on file prior to registration of any patients. Potential patients will be identified in the Oncology outpatient clinics

or by referrals from outside physicians. Patients who appear to be eligible for this trial will undergo the Informed Consent Process and be screened for eligibility utilizing the Eligibility Criteria. The original signed IRB approved Informed Consent Document and completed eligibility checklist will be forwarded to the School of Nursing designee for registration in the OnCore® database.

Study data will be collected and stored in OnCore®, developed by Forte Research Systems, Inc. (www.forteresearch.com). OnCore® Enterprise Research is a comprehensive, web-based, Clinical Trial Management System (CTMS) which utilizes an Oracle database. It has been licensed by Indiana University (IU) to support the operations and data capture of clinical research trials.

The system has been installed and configured within a HIPAA-aligned, Information Technology (IT), operations center supported by IU's IT organization, University Information Technology Services (UITS).

OnCore® provides users secure access with unique IDs/passwords and restricts access by assigned roles, from any location, to record, manage, and report on data associated with the operation and conduct of clinical trials.

The system is comprised of three specific applications—Clinical Research Management (CRM), Biospecimen Management (BSM), and Unified Registries Management (URM). Indiana University leverages OnCore® to support clinical research operations specifically as it relates to the following functions/processes: electronic Scientific Review Committee (SRC), regulatory management, protocol and subject life cycle management, coverage analysis, study financials management, subject registration and visit management, subject safety monitoring, protocol deviation monitoring, study auditing and monitoring, electronic data management, correlative study sample management, specimen banking and management, registries management, effort tracking, and reporting.

8. STUDY PROCEDURES

8.1 Recruitment and Consent

Subjects will be recruited using targeted mailings and direct contact. Similar to our pilot study, we will recruit in-person consecutive BCS who are being seen for care at the Indiana University Health Systems clinics including the IU clinics on campus (IUSCC) (including Eskenazi Hospital) and the associated Northside clinic in Carmel, IN.

We will also recruit through mailings. Similar to our pilot, we will use: (1) the IU Cancer Center tumor registry's 4,111 potentially eligible BCS, who fit our revised eligibility criteria and the (2) the Indiana Clinical and Translational Sciences Institute patient registry which has over 1,975 potentially eligible BCS. We will review lists to ensure that no duplicate inquires will be sent to potentially eligible BCS.

For in clinic recruitment, Dr. Schneider (co-I) or designee will get permission from patients to allow project staff to enter the patient's room during a clinic visit to introduce the study.

Introduce study and screen for eligibility/interest
For in clinic recruitment, the project recruiter then sequentially approaches each woman at the end of her clinic visit with the physician and describes the purpose and nature of the study.

For those that contact our office in response to a mailing, study staff will discuss the study requirements and screen for eligibility (phone or in person. Those determined to be ineligible due to depressive symptoms will be referred to their attending physician for follow-up.

Distribute study information: Following screening, study staff will send or hand out a study packet. Packets will contain a cover letter with contact information; a study brochure; copies of the informed consent statement and HIPAA-mandated authorization to allow use of protected health information; and a stamped, addressed envelope for returning the signed consent and authorization forms.

Obtain informed consent: Women who are eligible and interested will be consented in person in the clinic. Those women who do not return a signed consent will receive a phone call one week following their screening date to verify interest in participating and provide additional information if needed. Interested women will be instructed on the consent process. Informed consent will follow the requirements of the university's institutional review board

Eligibility/Baseline Assessment: After the signed written consent and HIPAA authorization forms are received, research staff will telephone the participant and arrange a mutually convenient appointment. Assessments will be completed in a private room at the university. First, eligibility will be confirmed via self-report by the participant.

If ineligible, the subject will be thanked for her time and interest in participating.

If eligibility is confirmed, the appointment will continue, and the other baseline assessment measures will be administered. Once the neuropsychological assessment and questionnaires are completed, the tester will review them and obtain data from the participant on any missing items

Randomization: Building on our pilot studies, BCS will be randomly assigned to one of two groups: BrainHQ cognitive training or attention control. Assignments will be in a random order generated by a computer using blocks of 8, to ensure filling of treatment groups. Randomization will occur as close to the start of the training sessions as possible to minimize study drop-out.

Neuropsychological testing, completion of questionnaires and collection of a blood sample for BDNF will be collected at two time points during the study. Baseline (T1) data will be collected prior to the initiation of the intervention or attention control computerized training. Follow up assessments and BDNF blood sample will be collected post-intervention within 90 days of completing the intervention or attention control computerized training (T2)

Serum for BDNF analysis and all biomarkers that are part of this study will be prepared by laboratory services at IU and will be securely and confidentially (blood sample code) stored in the Analyte Laboratory within the Translation Core of the Center for Diabetes and Metabolic Disease under management of Dr. Considine (Co-I). The BDNF serum levels will be batch analyzed following collection of all samples following the manufacturers' ELISA protocol. The ELISA assay has standards ranging from 7.8 to 500 pg/ml BDNF (this is the possible range for all samples).

The study will also examine biomarkers that can affect brain functioning including neurotropic factor, proinflammatory cytokines, cortisol, and dehydroepiandrosterone (neuro steroid) DHEA.

8.2 Intervention

The baseline assessment will be completed and then the participant will be randomized to computerized cognitive training or attention control group. An immediate post-test will be

completed, which will be 10 weeks after baseline (10 weeks for intervention within 90 days for completing the post-intervention assessment). The first visit will last about 1-hour and all other visits should last about 50 minutes.

At baseline, participants will provide demographic, clinical and treatment information, questionnaire data, blood sample, and complete a neuropsychological assessment administered by a trained and blinded tester. All other assessments will proceed in the same manner; however, demographic and treatment information will not be re-assessed. The medical record of BCS's will be examined for purposes of verifying disease and treatment information, including types and dates of treatments received (surgery, radiation, chemotherapy, tamoxifen and/or aromatase inhibitors). Data will be linked to participants through the use of a unique study-specific identifying number. Only persons on the research team will have access to the data. The neuropsychological tester will remain blinded to the randomization of the participants. All data are collected for research purposes only.

Cognitive Training: As tested in our pilot, the Brain HQ program is designed to enhance specific areas of cognitive functioning that will be tested in this study. The goals of the Brain HQ program are to improve visual processing speed, learning and memory and attention. The exercises include time-order judgment, discrimination, spatial-match, forward-span, instruction-following, and narrative-memory tasks.[97] This program systematically reduces the stimulus duration during a series of increasingly difficult information-processing tasks presented via computer. The exercises automatically adjust to user performance to maintain an 85% correct rate. The program will include 4 hours per week over a 10-week period for a total of up to 40 hours. We have support from the original developer and Posit Science. For the purposes of this trial, any participants who do not complete the total of up to 40 hours will not be counted as deviations.

BrainHQ uses five tasks in the form of computer games designed to improve memory, processing speed, attention, working memory and executive function including:

1. Sweep Seeker: The person is asked to clear the rows of blocks presented on the screen, either by moving them into horizontal or vertical blocks that have identical color. The goal is to refine and increase the response of primary visual cortex neurons and to enable the person to increase speed and accuracy of visual processing (executive function) and visual memory.
2. Bird Safari: The user is first presented with a target bird. Subsequently, a group of birds is presented in the peripheral vision and then disappears when the trial begins. The user selects the section of the screen where the target bird appeared. The presentation speed adapts with user performance (i.e. better performance = faster presentation). The goal is to improve speed and accuracy of object identification in peripheral vision and improve visual precision important for improving memory.
3. Jewel Diver: The person is first presented objects (jewels) on the screen. The objects are then covered with occluders (bubbles) and then identical distracters are presented. The objects move around in screen and when the movement stops, the user chooses the occluders that cover the jewels. The number of jewels adapts to performance (more jewels = better performance). The goal is to improve divided visual attention, sustained visual attention, visual working memory, and visual precision.
4. Master Gardener: The person is presented a series of target stimuli and distracters which are presented at one time and then disappear. The locations of the stimuli are marked by icons, and the user choses the icons where the target stimuli were once located. The goal is to increase speed and accuracy as well as the ability to extract information accurately.

5. Road Tour: The person is presented with a target vehicle briefly in both the center of the screen and in one of eight locations in the periphery. Two vehicles are then presented briefly in the center of the screen, one of which is the target vehicle. The user must identify the location of the target vehicle in the periphery as well as identify which was the target vehicle that appeared in the center. The goal of this activity is to improve divided attention and ability to extract information and discard irrelevant information from peripheral vision.

Attention Control: Control participants will be asked to complete activities on the computer. The program offers a choice of activities that will consist of crossword puzzles and word jumbles. Attention Control: Computer-based General Cognitive Stimulation Intervention (Computerized Crossword Puzzles): The program offers a pre-determined set of computerized crossword puzzles (www.bestcrosswords.com; http://zone.msn.com/en/crossword; Accessed *09-15-2015*). The site has over 100,000 puzzles and can be accessed easily via the web and are free to users. The computerized crossword puzzles do not provide for progressive challenges of increasing speed, visual field size, number of distractors or degree of difficulty of targeted stimulus differentiation. Training: Participants will be instructed to perform this active attention control intervention 4 hours per week over 10 weeks for a total of up to 40 hours, the same as BrainHQ.

The rationale for this attention control program is (1) it has been routinely and successfully used in other NIH-funded cognitive training trials, (2) it has not shown cognitive benefit in previous research studies,[44,98] and (3) previous experience by our team and others have shown that it is an appropriate computerized attention control alternative.[43,44] The delivery format, number of sessions, and setting all parallel the intervention of up to 40 hours over 10 week period. Table 1 describes the difference between the **Brain HQ** intervention and the attention control cognitive training interventions.

Based on the randomization, the project manager will provide verbal and written instruction for accessing and using the program and the minimum amount of practice required. BrainHQ and computerized attention control programs will capture the date and time the participants participate in the study.

Table 1 Comparison of BrainHQ to Attention Control

Element	Computerized Cognitive Training using BrainHQ	Attention Control Computer-Based General Cognitive
Visual stimuli	Intensive & repetitive with increasing visual stimuli	None
Complexity of stimuli	Progressively increased speed & processing of stimuli with increasing distractions	No Progressive Challenge
Cognitive demand	Tailored; Training adjusted by computer to 85% of individual's threshold	Not tailored; not adjusted or tailored for individual threshold
Visual attention & memory	Directed attention with each exercise, precision	No directed attention from computerized intervention
Novelty	Individualized feedback and rewards built in to respond to the participant, game features to improve satisfaction	Feedback and rewards not provided, may incur some satisfaction on their own

Post Intervention: A follow up assessment will be conducted immediately post intervention (T2). Based on our pilot study, the post-intervention assessment and BDNF blood draw will be completed within 90 days of completing the intervention (T2) training or attention control sessions.

Procedures for Monitoring Treatment Fidelity: As in our pilot, procedures for monitoring treatment fidelity will

be guided by the Treatment Fidelity Checklist.[99] Both groups have been standardized in dose (length and content) and delivery method (in-home). Intervention dose will be carefully monitored using the computer software built within BrainHQ and Rescue Time software for the active attention control (total time on task). These variables will be examined and used in the analysis. The PI will be responsible for oversight of treatment fidelity The neuropsychological tester will be blinded to group status. The project manager will ensure the participants understand and are utilizing the program. Treatment dose and content will be carefully monitored through the InSight program .

Qualitative assessment: individual interviews will be conducted over the phone with members of the intervention group to understand the perceived facilitators and barriers to use of the intervention. All interviews will be conducted after the intervention, voice recorded digitally and labeled with a patient identification number.

Accrual & Retention: Several steps will be taken to ensure high rates of accrual, retention, and representation of minority BCS. These include (1) using culturally appropriate printed study information;[100-102] (2) contacting potential subjects in person in the clinic, which has been shown to be preferred over unsolicited telephone calls [101] and to be more effective in recruiting minority subjects;[103] and (3) providing participant incentives of $20.00 for every assessment completed ($40.00 for both) to offset subject burden.

9. MEASURES

Table 1 displays the **quantitative data** collection plan and details of measures. The neuropsychological battery has been shown to be reliable and valid. [104]Based on our pilot, estimated completion time for the initial baseline assessment will be 1 hour with each follow-up session lasting approximately 50 minutes. **Qualitative assessment**: individual interviews will be conducted over the phone with members of the intervention group to understand the perceived facilitators and barriers to use of the intervention. All interviews will be conducted after the intervention, recorded digitally and labeled with a patient identification number. This will be done only one time and will last up to 30 minutes.

Table 2. Schedule of Quantitative Measures

		No. Items/ (Potential range)				
Variable	Instrument (Measure)	T1	T2	Instrument Range	Reliability	Score
	Screening					
Perceived Cognitive Function	Numeric rating scale (0 to 10)	X		0-10	n/a	↓
Depression	PHQ-9[107,108]	X			0.84	↓
	Aim 1: Satisfaction and Acceptability					
Satisfaction	Client Satisfaction Questionnaire		X	8-32	0.90-0.94†	↑
Acceptability	Acceptability Scale		X		NA	↑
	Aim 2 Subjective Cognitive Measures					
Perceived Cognitive Function	ŧPROMIS – Applied Cognition- Abilities	X	X	33 (33-165)	0.97†	↑ ↓

	ǂPROMIS - Applied Cognition Gen. Concerns [16,120]	X	X	34 (34-170)		
	Aim 4 Objective Cognitive Measures					
Memory	Rey Auditory-Verbal Learning Test [109] Rivermead Behavioral Memory Test[110]	X X	X X	15 words, 5 trials (0-75) N/A		
Speed of Processing	Symbol Digit	X	X	7-500ms	0.78* 0.60*	↑ ↑
					0.71-0.88	↓
Working Memory	Wechsler Adult Intelligence Scale IV – Digit Span[116]	X	X			
Executive Function - Language	Controlled Word Association[117]	X	X	#words/1min	0.96	↑
	Aim 3 Other Outcomes				>.70	↑
Work Ability	Work Ability Index (WAI) [123-125]	X	X	7 (7-49)	0.98† 0.97† 0.99†	↓ ↓ ↓
Quality of Life	Quality of Life-Cancer Survivors (QOL-CS)[126]	X	X	41 (0-10 on 4 sub-scales)	0.66*	↑
	Exploratory Aim 4 Intervention Effect on BDNF				0.93†	↑
Serum BDNF levels	Serum BDNF –ELISA			X	X	Assays range: 7.8-500 pg/ml
	Intervention Fidelity Assessment & other symptoms				Within assay %CV at 334pg/ml =4.7% Within assay %CV 825pm/ml = 3.4%	↑
Dose	Time Spent each session – Computer					N/A
Depressive Symptoms Anxiety Fatigue	PROMIS-Depression Short Form [121] [122] PROMIS-Anxiety Short Form [122] PROMIS-Fatigue Short Form[121]	X X X	X X X	8 (0-40) 8 (0-40) 8 (0-40)		

10. DATA ANALYSIS

Descriptive statistics and assessment of internal consistency reliability will be computed for all variables. **Aim 1 Feasibility and Satisfaction:** Descriptive statistics and frequencies will be used to summarize the Client Satisfaction Questionnaire and Acceptability Scale. The two groups will be compared on the mean of each item using the *t* test or Wilxocon rank sum test if the parametric assumptions are violated. **Qualitative Analysis:** A conventional content analysis approach, which aims to summarize the informational contents of the data, will be used.[126,127] Common themes across all the participants' data will be identified and organized into clusters and categories. **Aims 2-4:** A linear mixed-effects models[128] to analyze repeated-measures

ANCOVA, to compare the effects of cognitive training to attention control will be used. The dependent variables, cognitive performance measured post-intervention, will be the primary outcomes. The baseline cognitive performance will be adjusted for as a covariate. The other independent variables will be the fixed effect for training group (BrainHQ, attention control), the Time effect, and the interaction term of Time-by-Training Group. The primary test of interest will the Group effect, which compares the two randomized groups on the outcome. The second most important test will be the interaction test to determine whether change over time differs for the two groups. We will also assess the Time effect, which tests whether scores generally changed in one direction for both groups combined. In addition, to ensure equivalence across groups potential covariates will be adjusted for in the models on which the various intervention and control groups significantly differ after random assignment at a liberal p-value of <.10. Effect sizes between the two groups will be computed as differences between adjusted means divided by pooled standard deviations. The significance level will be <.05 for all tests of hypotheses. **Aim 5** provides the estimation of the effect of cognitive training on serum BDNF. Similar to Aims 1 and 2, a GLMM will be fitted to the data to estimate this effect, while controlling for potential known confounding effects including, age, education, smoking status, body mass index, medications, physical activity (per DUKE Activity Status Index[129]) that may influence BDNF interpretation[130] prior to hypothesis testing; although the RCT design will likely balance these factors.

Power analysis: We are adequately powered for estimating effect sizes or preliminary efficacy (Aim 2). Sample size is based on Aim 2 preliminary tests of post-intervention efficacy of the intervention on continuous outcomes. A difference between means equal to 0.80 standard deviations represents a large effect size, a medium effect size is 0.50, and a small effect size is 0.20.96 Using the Nquery software, a sample size of 30 in each group will provide 86% power for a two-sided t test to detect a large effect size of 0.80 when alpha is .05, to detect small or medium effect sizes.

Methods for Handling Missing Data and Dropouts: The GLMM approach to analysis allows use of all available data, including from participants who have incomplete (i.e., partially missing) data. We will compare those who dropped out to those who completed the study on various demographic and treatment factors and on intervention group membership. To the extent that differences exist, we will describe this bias and its potential effects on the results of our analysis. Additionally, we will attempt to determine missing data patterns, and, if cell sizes permit, will incorporate this information into the analyses by re-running the GLMM with incorporation of the missing pattern as a nominal covariate.

Additionally, the influence of treatment dose (i.e.: sessions completed) will be evaluated to determine if it should be included as a covariate in the GLMM. Participants will be randomized only after completing baseline assessment. There are only two possible missing data patterns: baseline and immediate post only.

11. DATA INTEGRITY AND SECURITY

All documentation will be stored on a limited-access university server or in locking file cabinets in a limited-access, locked project office. All electronic databases housing subject data will be password-protected with access limited to study personnel only. Identifying information is separated from all data provided by participants through the use of a unique identification code assigned by study personnel to each subject.

Analysis of objective neuropsychological data will be monitored for quality assurance. Personnel who conduct the neuropsychological assessments (tester) will complete a standardized

instruction course and will be certified to deliver the assessment based on criteria developed by Dr. Unverzagt (Co-I).

All data entry will be done by trained personnel. Databases will be constructed to include forms for data entry that mirror questionnaires and have restricted field ranges and values to prevent errors. In addition, quality of data entry will be monitored by the Project Manager, who will randomly select patient files to be double-entered and will periodically generate reports for the entire dataset to identify outliers, missing data, or other problems. All data will be imported into SAS data sets for analysis. Analyses will include only summaries of data; personal identifiers will be omitted

12. STUDY TIMELINE

Study Timeline	May	June	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr
Study start up (hiring, training, finalize all study protocols)	X											
Enrollment and baseline data collection		X	X	X	X	X	X	X	X			
Randomization, delivery of intervention/control		X	X	X	X	X	X	X	X	X		
Follow-up data collection, data entry and management		X	X	X	X	X	X	X	X	X	X	
Analyze preliminary, baseline and follow-up			X	X	X	X	X	X	X	X	X	X
Dissemination: literature review, theory review, intervention description, baseline and final study findings			X	X	X	X	X	X	X	X	X	X

13. RISKS TO SUBJECTS

Potential risks associated with study participation are minimal. Subjects may experience: (a) bruising, bleeding, soreness or rarely, fainting of infection as a result of venipuncture for collection of the blood samples (b) psychosocial risks and (c) breach of confidentiality. Risks in the psychosocial realm would involve any anxiety or distress that may result from participation in the scheduled study assessments and/or phone interview. Based on our prior work with similar assessment protocols, we anticipate that any negative psychological reactions will be uncommon and generally very mild. There is always some risk that a woman's responses during the study will become known to others outside the research project staff. No unusually sensitive information is being collected in our study; for example, we are not collecting information on sexual behavior or criminal behaviors, or substance abuse.

Steps will be taken to minimize any potential risks associated with study participation.

To minimize bruising, bleeding, soreness or rarely fainting or infection as a result of venipuncture. Our experienced research staff is trained and certified in phlebotomy. They will apply universal precautions when drawing blood to reduce the risk of infection and will take steps to minimize discomfort to subjects including application of pressure on the site following

needle withdrawal. Additionally, subjects will be asked to remain in a sitting position for five minutes after blood has been withdrawn and will be observed for any untoward effect.

To minimize any psychosocial or physical risks, participants will be told that they have the option of discontinuing their study participation at any time during the course of an assessment session or at any point during the study. Research assistants will be trained to identify unusual distress and will notify the PI, who will conduct follow-up assessments and refer participants to their healthcare provider if necessary.

To minimize risks associated with breach of confidentiality we will assign each study participant a unique identification number and using this to identify all study data records. A single list connecting the study identification number with each participant's name will be kept in a password-protected database on a limited-access university server. Furthermore, all study data records, or digital recordings will be maintained in locked file cabinets and/or password-protected databases on limited-access university servers. Access to study data records will be furnished only to individuals who are members of the project research team. All personnel who are involved in the design or conduct of this research will have successfully completed human subjects training.

For women who exhibit extreme scores on the PHQ-9 brief depression screen we will adhere to the following PHQ-9 Referral Algorithm: Score ≥ 15, negative response to self-harm item: Refer to physician for follow-up; Score ≥ 15 positive response to self-harm item: Keep patient on the telephone, assess emergent needs of patient. If immediate risk is low, refer to suicide hot line and inform patient you will be notifying her oncologist for follow-up. If immediate risk is high, call 911, refer to suicide hot line, and inform patient you will be notifying her oncologist for follow-up.

14. POTENTIAL BENEFITS

Subjects may benefit from participating in cognitive training with improvement in memory performance and/or speed of processing. This research will provide information about the efficacy of the BrainHQ cognitive training intervention in BCS. This research could also provide a non-pharmacological alternative to address cognitive impairment in a generally younger population of cancer survivors who currently have limited or no other treatment options. Risks of participation are minimal.

Importance of the Knowledge to be Gained:

Knowledge will be gained on the efficacy of a commercially available cognitive training intervention that may help improve cognitive impairment in cancer survivors. This study will provide the necessary evidence regarding the use of cognitive training in breast cancer survivors. Such improvement is essential to helping improve BCS quality of life. Risks in this study are minimal. Findings will provide empirical evidence for or against the use of the cognitive training intervention for improving memory performance and processing speed. Importantly, either positive or negative findings will provide guidance for clinicians' recommendations and consumers' treatment selections relative to the use of this type of advanced cognitive training This research study will provide efficacy data about the cognitive training intervention and will offer a non-pharmacological alternative to improving cognitive performance in breast cancer survivors, who have limited or no other treatment options. In addition, if efficacious this cognitive training program could be tested in a broader population of cancer survivors incurring similar cognitive deficits

15. PATIENT CONSENT AND PEER JUDGMENT

The protocol and informed consent form for this study must be approved in writing by the appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator (housed in the Clinical Trials Office) and are subject to inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 90 days of study completion or termination.

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

16. DATA AND SAFETY MONITORING PLAN

This study will be conducted in accordance with the IU Simon Cancer Center Institutional DSMP for **Low Risk Trials.**

Investigators will conduct continuous review of data and subject safety. **Quarterly review meetings** for low risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). **Quarterly** meeting summaries should include review of data, the number of subjects, significant toxicities as described in the protocol, and responses observed. Study teams should maintain meeting minutes and attendance for submission to the DSMC upon request.

Data and Safety Monitoring Committee

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study annually to review overall trial progress, toxicity, compliance, data integrity, and accrual per the Institutional DSMP.

Furthermore, the DSMC conducts an administrative review of serious adverse events (SAEs), deviations, reportable events, and any other outstanding business. Major issues may require further DSMC review or action.

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the subject warrant early closure of the study, the DSMC Chair and Compliance Officer must be notified within 1 business day via email, and the IRB must be notified within 5 business days. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

Study Auditing and Monitoring

All trials conducted at the IUSCC are subject to auditing and/or monitoring per the Institutional DSMP. Reports will be reviewed by the full DSMC at the time of study review.

Data Management/ Oncore Reporting Requirements

The DSMC reviews data and study progress directly from Oncore; therefore, timely data entry and status updates are vital. Study data must be entered within Oncore promptly, no later than one week from study visit occurrence. Subject status in Oncore will be updated in real time, as this may affect overall trial enrollment status. Global SAEs and deviations will be reviewed on a monthly basis by the DSMC Chair directly from Oncore.

Study Accrual Oversight

Accrual data will be entered into the IU Simon Cancer Center OnCore system. The Protocol Progress Committee (PPC) reviews study accrual twice per year, while the PPC coordinator reviews accrual quarterly.

Oncore Safety Reporting
In addition to protocol- and regulatory-required safety reporting, all serious adverse events (SAEs) will be captured in the Oncore system within 1 business day of notification. Initial SAE reporting will include as much detail as available, with follow-up to provide complete information. Attributions will be assessed to study drugs, procedures, study disease, and other alternate etiology.

Protocol Deviation Reporting
Protocol deviations will be entered into OnCore within 5 days of discovery and reviewed by the DSMC Chair on a monthly basis. Findings will be reported to the full DSMC at the time of study review. For serious or repetitive protocol deviations, additional action may be required by the DSMC.

17. ADVERSE EVENTS

Adverse Event (AE):
An adverse event is defined as untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. An adverse event can be ANY unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an intervention, whether or not considered related to the intervention (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite'). Adverse events will be graded according to the NCI Common Toxicity Criteria, Version 4.0.

For this study, an Adverse Event will be defined as any reaction or undesirable event that occurs while a subject is on the research protocol whether or not it is considered relate to the study intervention (cognitive training). Such events could include illness, signs, symptoms, or abnormal laboratory tests that have appeared or worsened during the course of the trial regardless if any causal relationship to the study can be made.

Serious Adverse Event (SAE):
A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death or ANY death occurring within 30 days of a biopsy procedure (even if it is not felt to be related).
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization ≥ 24 hours or prolongation of existing hospitalization
    - NOTE: Hospitalizations that are not considered SAEs are:
        - Hospitalization planned prior to biopsy procedure
        - Hospitalization of less than 24 hours
        - Hospitalization for elective treatment of a pre-existing condition unrelated to biopsy procedure.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed

in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

Attribution: An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily *"caused by a therapeutic intervention"*. After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Relationship	Attribution	Description
Unrelated to investigational intervention	Unrelated	The AE is clearly **NO**T related
	Unlikely	The AE is **doubtfully related**
Related to investigational intervention	Possible	The AE **may be related**
	Probable	The AE **is likely related**
	Definite	The AE **is clearly related**

18. SAE REPORTING

18.1 SAE Reporting to the IRB:

Unanticipated problems involving risks to subjects or others will be reported **within 5 days** of becoming aware of the event to the IRB if they:

- unexpected;
- related or possibly related to participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the serious adverse event does not meet all three (3) criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it should be reported at the time of continuing review

18.2 SAE Reporting to the IUSCC Data Safety Monitoring Committee:

Regardless of study sponsorship, the study team must enter all initial and follow-up SAE, expedited, and noncompliance reports into OnCore® for review by the DSMC chair and/or coordinator. Expedited reports may include IRB Prompt Report Forms and additional SAE forms as required by the sponsor. When follow-up information is received, a follow-up report should also be created in OnCore®. This DSMC reporting requirement is **in addition to any other** regulatory bodies to be notified (i.e., IRB, FDA, pharmaceutical company, etc.). The DSMC chair and/or coordinator will review all SAE, expedited, and noncompliance reports monthly.

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