Protocol: A Randomized Trial of Physical Activity for Cognitive Functioning in Breast Cancer Survivors: I Can! Improving Cognition After Cancer

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Principal Investigator: Sheri J. Hartman, PhD

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1.0 Study Objectives

This study examines the effects of a 6-month physical activity intervention on changes in processing speed and self-reported cognitive concerns among breast cancer survivors (N=250) at 3 and 6 months (middle and end of intervention) and 12 months (maintenance). Participants are randomly assigned to receive (1) a home-based physical activity intervention grounded in Control Theory and Social Cognitive Theory (Exercise group), or (2) a health & wellness attention-comparison condition (Health & Wellness group). At baseline, 3, 6, and 12 months, participants complete neurocognitive testing, questionnaires assessing self-reported cognition, a battery of psychosocial questionnaires, a non-fasting blood draw, the 3-minute Step Test, and wear an ActiGraph GT3X+ accelerometer for 7 days.

Primary Aim:

1. Investigate the impact of the physical activity intervention on changes in processing speed and self-reported cognition compared to the Health & Wellness attention-comparison condition.
    a. *Hypothesis: The Exercise group will show greater improvements in processing speed, assessed by neurocognitive testing, and self-reported cognition, during the 6-month intervention compared to the Health & Wellness group.*

Secondary Aims:

1. Investigate the impact of the Exercise group on maintenance of changes in cognition compared to the Health & Wellness group.
    a. *Hypothesis: At 12 months, the Exercise group will show greater improvements in processing speed, assessed by neurocognitive testing, and self-reported cognition compared to the Health & Wellness group.*
2. Examine candidate biological mechanisms and psychological mediators of intervention-related changes in cognition.
    a. Hypothesis: The Exercise group will have greater improvements in aging-related DNA methylation profile as well as reduced anxiety and depression compared to the Health & Wellness group, which will partially mediate the relationship between the intervention effect and cognition outcomes.

Exploratory Aims:

- Explore a dose-response relationship between changes in physical activity and fitness, objectively measured by ActiGraph accelerometer, 3-minute step test, and 30-second sit-to-stand test with changes in processing speed and self-reported cognition.
- Explore changes to other cognitive domains (memory, executive function, and attention), objectively measured with neurocognitive testing, in the Exercise group compared to the Health & Wellness group.

2.0 Eligibility criteria

Inclusion criteria:

- Female breast cancer survivors
- Age 40 years or older
- Completed active treatment (e.g., chemotherapy, radiotherapy) at least 6 months prior to enrollment
- Within 5 years of diagnosis of stage 1, 2, or 3 breast cancer
- Sedentary, defined as self-reporting less than 60 minutes of moderate to vigorous physical activity (MVPA), accumulated in 10-minute bouts, each week
- Self-reporting difficulties with cognition with a score of 4 or higher on a 0-10 scale

- Have a Fitbit compatible device (e.g., smartphone, computer) with Internet access
- Received chemotherapy and/or hormonal therapy (i.e., aromatase inhibitors, tamoxifen).

Exclusion criteria:
- Medical condition that could make it unsafe to participate in unsupervised physical activity, as determined by the Physical Activity Readiness Questionnaire, including self-reported neuropathy that interferes with ambulation, or unable to walk unassisted (e.g. uses a cane)
- Currently taking tamoxifen or an aromatase inhibitor that will be stopped in the next 6 months
- Unable to commit to a 12-month study.

3.0 Study Procedures

Recruitment

The primary recruitment method is through registry lists of breast cancer survivors from the California Cancer Registry and the UC San Diego Epic electronic medical record. Women are mailed a letter and flyer about the *I Can!* study and informed that the study team will reach out to them by phone or email, if they do not opt out by contacting the study office. In addition, study information is provided to oncologists at the UC San Diego Moores Cancer Center and surrounding area, UC San Diego clinics, and local cancer support and philanthropy groups so they can refer breast cancer survivors to the study.[40,54,55] All methods and procedures have been approved by the UC San Diego institutional review board.

Screening

Potential participants are first screened for eligibility over the phone. To reduce the likelihood of adverse events, participants are screened for factors that may increase risk of injury. Screener questions include the 10-item Physical Activity Readiness Questionnaire (PAR-Q)[53] and questions adapted from our previous trials.[41,56] The study physician advises on any medical questions that arise when screening for eligibility. Interested and eligible participants are then scheduled for an in-person orientation/measurement visit.

Orientation/Measurement (Visit 1):

At Visit 1, the first in-person visit (approximately 2-2.5 hours), study requirements are discussed and written informed consent is obtained. Participants then complete baseline measures including anthropometric measures, blood draw, neurocognitive testing, and psychosocial questionnaires (see Measures section). Participants are fitted with a hip worn accelerometer, an ActiGraph GT3X+ (ActiGraph, LLC), and instructed to wear it during waking hours for the next 7 days. Using protocols successfully employed in previous studies to ensure adequate ActiGraph wear, participants receive two reminder calls over the next 7 days. After wearing the ActiGraph for 7 days for at least 10 hours per day, participants return the device to the clinic at their randomization visit.

Randomization (Visit 2)

At Visit 2 (approximately 1.5-2 hours), participants' ActiGraph data is first screened for adequate wear time. If participants have sufficient wear time, they complete the final baseline measures, a 3-minute step test to assess cardiopulmonary fitness and a 30-second sit-to-stand test to assess lower-body strength. Participants receive $20 for completing the baseline measures.

Once all baseline measures are completed, participants are randomized using a 1:1 allocation ratio of Exercise group to Health & Wellness group. Randomization uses a permuted-block design that includes strata for treatment with chemotherapy (Yes or No) and treatment with hormone therapy (Yes or No). Randomization lists are generated by the study statistician. Measurement staff are blinded to group assignments. After randomization, participants meet with a health coach to review the expectations and requirements for their randomly assigned group.

3, 6, and 12 Month Measurements (Visit 3, 4, & 5)

Participants in both groups are mailed an ActiGraph and asked to wear it during the 7 days prior to each follow-up measurement visit, using the same protocols specified in Visit 1 to ensure adequate wear. At each measurement visit (approximately 2-2.5 hours), participants repeat the measures that were completed at baseline including neurocognitive testing, self-reported cognition, psychosocial measures, blood draw, anthropometric measures, step test, and sit-to-stand test (See Measures section). Participants receive $50 for completing each visit and a $50 bonus for completing all three follow-up visits (3, 6, and 12 months).

4.0 Treatment conditions

Exercise Group

The exercise intervention is based on Control Theory[57-59] and Social Cognitive Theory (targeted theoretical constructs italicized below).[60] Participants start with an in-person meeting with their health coach where they receive a Fitbit, an electronic activity tracker for *self-monitoring* physical activity (see details below). To promote *accountability*, participants are informed that their health coach can see the physical activity data collected by the Fitbit. Fitbit data is used to support *performance feedback* and *reviewing goals* during contacts with their health coach. Using motivational interviewing techniques to increase *self-efficacy* and promote *intention formation*, a goal with a specific plan for meeting that goal is set. Participants discuss with their health coach ways to gradually increase their exercise over time to meet the study goal of at least 150 minutes of MVPA per week.[61] To ensure that participants know what moderate intensity activity feels like and to increase *behavioral capability*, participants are taken on a 10-minute walk at 50 to 70% of their age-based maximum heart rate (based on CDC guidelines). To ensure that participants are increasing their activity level safely, the health coach covers key safety information including the importance of gradually increasing activity, stretching, and what to do when you are sick. Participants set a specific, personalized goal. They can choose any activity of interest that increases their heart rate to their target heart rate goal and that can be sustained for at least 10 minutes at a time. Based on our previous studies, we anticipate the most common activity to be walking, with other activities including exercise classes, hiking, biking, and gym equipment (e.g., elliptical, treadmill).

Brief phone calls (15-20 minutes) are scheduled every other week during the first 6 months to review Fitbit data, discuss progress towards goal, revise goal, and provide support. Each call also covers a specific topic to support behavior change. To support the calls, the health coach accesses participants' Fitbit data through a web-based database, Fitabase (Small Steps Labs, San Diego, CA). Through Fitabase, the health coach can see graphs of daily light, moderate, and vigorous physical activity, date of last Fitbit sync, and Fitbit battery level. The Fitbit data is used to support the health coach calls by identifying days with low activity where activity could be added, and days with high activity to reinforce what is working well. In addition, the health coach checks Fitabase once a week so that participants can be proactively reached out to by their health coach as needed. In general, participants receive a text or email from their health coach if: 1) their active minutes on their Fitbit are 20% lower than their personal goal; 2) their active minutes are 20% higher than their personal goal; or 3) they have met their goal when

they had not previously been achieving their goal (i.e., 4 weeks without achieving goal). This method of proactively reaching out to participants, rather than waiting for scheduled phone calls, was highly successful and extremely well-liked in our previous study.[41] Participants are encouraged to reach the 150 min/week of MVPA by 3 months (consistent with the American College of Sports Medicine guidelines for physical activity for cancer survivors), and then maintain that level of activity for the next 3 months.

Participants also receive static emails twice a week throughout the 6-month intervention. The emails further target components of Control Theory and Social Cognitive Theory with content including: 1) self-monitoring physical activity; 2) how to get social support for being active; 3) online resources, including how to find places to be active and exercise videos; and 4) tips on how to change outcome expectations and use one's thoughts for exercise motivation. Each week, participants receive one in-depth email addressing these components and one brief tip of the week email.

During the maintenance period (months 6-12) participants are asked to continue wearing and syncing their Fitbit. Emails with theory-based content and reminders to wear and sync their Fitbit are sent every other week. They also receive brief check-in calls (10-15 minutes) once a month from their health coach to support continued progress towards their personal exercise goal. The health coach uses motivational interviewing techniques to guide the content of each monthly call and support maintenance of activity level.

<u>Health & Wellness Group</u>
Participants start with an in-person meeting with their health coach to discuss breast cancer and cognition, general brain health, and age-related brain changes. They are then presented with the list of topics that are covered in the Health & Wellness group to identify topics of most interest that the health coach will focus on during the phone calls. Participants in the Health & Wellness group receive brief phone calls (15-20 minutes) and emails on the same schedule as the Exercise group. Calls and emails consist of a variety of topics to support overall wellness, such as brain health, stress management, nutrition, and sleep/insomnia. Participants are encouraged to set a general goal related to the topic of the week (e.g., try a stress management technique discussed during the call). If a participant expresses concerns and challenges to meeting their goal, the health coach will reach out by text or email to check in between calls, attempting to keep contact time similar between the two treatment groups. Each week, participants receive one in-depth email addressing a health topic and one brief tip of the week email.

During the maintenance period (months 6-12), participants receive monthly check-in calls (10-15 minutes) and emails every other week from their health coach to discuss health topics from the emails, maintain connection to the study, and increase retention at 12 month measurement.

Week	**Description of *I Can!* study activities**
-1	Initial phone screening for breast cancer eligibility, physical activity level, cognition, etc.
0	**Orientation/Measurement** Written informed consent Objective & self-report cognition measures, questionnaires, blood draw, height & weight, medical chart abstraction, given an ActiGraph to wear on the hip for the next 7 days
1	**Randomization** Return ActiGraph, step test, sit-to-stand test, & randomized to Exercise group or Health & Wellness group

	Physical Activity Intervention	Health & Wellness Condition
	45 min in-person intro to the Exercise group: • Taught how to use and sync Fitbit • Guided 10 min walk at moderate intensity • Personalized Weekly Goal • Discuss topic of the week: Self-monitoring, Exercising safely, & Exercise resources	45 min in-person intro to Health & Wellness group: • Review menu of topics to be covered • Participants chooses topics of interest and receives handouts on each topic (sample topics below) • Discuss topic of the week: Brain Health
1-24	Emails 1-2 times a week with reminders to be active & use Fitbit and information & resources for exercising	Emails 1-2 times a week on Health & Wellness topics
3, 5, 7, 9, 11	20 in phone counseling: • Review Fitbit data & revise goal and action plan • Discuss topic (Week 3: Building motivation; Week 5: Setting goals; Week 7: Social support; Week 9: Slips; Week 11: Benefits of exercise for cancer survivors)	20 min phone counseling: • Discuss any questions from the previous call • Discuss topic (Week 3: Social connections; Week 5: Healthy eating; Week 7: Stress management; Week 9: Balance exercises; Week 11: Time management)
11	Start wearing ActiGraph for 3 Month measurement	
12	**3 Month Measurement** Objective & self-report cognition measures, questionnaires, blood draw, weight, step test, sit-to-stand test, return ActiGraph	
13, 15, 17, 19, 21, 23	20 min phone counseling: • Review Fitbit data and progress towards goal • Revise goal and action plan • Discuss topic (Week 13: Problem solving barriers; Week 15: Time management; Week 17: Rewards; Week 19: Talking back to negative thoughts; Week 21: Strength and core exercises; Week 23: Maintenance & Holidays/vacations)	20 min phone counseling: • Discuss any questions from the previous call • Discuss topic (Week 13: Keep your mind active; Week 15: Sleep; Week 17: Building healthy recipes; Week 19: Talking back to negative thoughts; Week 21: Nutrition labels; Week 23: Maintenance of healthy habits)
23	Start wearing ActiGraph for 6 Month measurement	
24	**6 Month Measurement** Objective & self-report cognition measures, questionnaires, blood draw, weight, step test, sit-to-stand test, return ActiGraph, satisfaction survey	
28, 32, 36, 40, 44, 48	Maintenance Period: • Continue to wear and sync Fitbit • Monthly check-in phone calls • Emails every other week with reminders to be active & use Fitbit, information and information & resources for exercising	Maintenance Period: • Monthly check-in phone calls • Emails every other week on Health & Wellness topics
51	Start wearing ActiGraph for 12 Month measurement	
52	**12 Month Measurement** Objective & self-report cognition measures, questionnaires, blood draw, weight, step test, sit-to-stand test, return ActiGraph	

Table 1. Measurement and intervention schedule

5.0 COVID-19 Impacts on the Protocol

Due to the COVID-19 pandemic, from March 19, 2020 through May 31, 2020, all in-person assessment and randomization visits were stopped in guidance with UC San Diego research

policies and California state orders. Since intervention contacts for both study groups are by phone, intervention delivery was able to continue without interruption. Additional participant resources and information regarding COVID-19 that are appropriate for each study group were added to the respective intervention calls. To minimize data loss during the pause of in-person visits, enrolled participants who become due for their 3 month assessment visit during office closures were asked to complete measures remotely. NIH Toolbox measures were obtained through Zoom video conferencing using the NIH Toolbox recommendations for remote delivery.[62] Participants were mailed the ActiGraph to objectively measure physical activity per protocol on the due date. Survey measures were emailed to participants on the due date through REDCap, a secure, web-based platform designed to support data capture for research studies.[63] For the 6 month assessment, only the ActiGraph and surveys were completed remotely. Eleven participants who came due for their 6 month visit during the closure had their active intervention period extended (calls every 2 weeks continued for both study groups), and were brought in for an in-person visit as soon as the clinic re-opened June 1, 2020. Participants whose in-person visit occurred more than 3 weeks after their last ActiGraph and surveys were remotely completed were asked to repeat the ActiGraph and surveys at the time of the in-person visit. No 12 month assessments were due during the COVID-19 closure.

Minor protocol changes were enacted to resume in-person visits. All questionnaires are being completed at home through REDCap surveys to reduce the amount of time in clinic. In addition, the 3-minute step test and 30-second sit-to-stand test were paused until it is safe and allowable to conduct visits without masking. All masking, physical distance, and sanitation protocols required by UC San Diego are being followed. The study protocols may continue to shift to support remote delivery, as well as home visits and in-home phlebotomy, to respond to the changing requirements related to the COVID-19 pandemic to maintain safety for participants and study staff.

6.0 Measures

The primary outcomes are objectively measured processing speed and self-reported cognition, which are assessed at baseline, 3, 6, and 12 months. Processing speed is measured with the Oral Symbol Digit test from the NIH Toolbox Cognition Domain (nihtoolbox.org),[64,65] which was developed by the NIH's Blueprint for Neuroscience Research to create a standard instrument to measure cognition in prevention and intervention trials. The measure is a computer-based version of the Wechsler Adult Intelligence Scale Digit-Symbol-Coding test and has been validated and normed in individuals age 3 to 85. The primary self-reported cognition measure is the Patient Reported Outcomes Measurement Information System (PROMIS) Cognitive Function scale that uses Computer Adaptive Testing to assess individuals' perceptions of deficits in the areas of mental acuity, concentration, verbal and nonverbal memory, and verbal fluency, as well as perceived changes in these cognitive functions.[66]

Secondary outcomes focus on the psychological and biological mechanisms. Proposed psychological mechanisms of anxiety, depression, fatigue, and physical functioning are measured at baseline, 3, 6, and 12 months. The PROMIS-Cancer scales for anxiety, depression, fatigue, and physical functioning, developed for cancer survivors, is administered using Computer Adaptive Testing.[67] The proposed biological mechanism, aging-related DNA methylation, is also measured at baseline, 3, 6, and 12 months. Non-fasting blood is drawn by certified phlebotomists at UC San Diego Moores Cancer Center. Serum, EDTA plasma, and buffy coat are prepared from the collected blood; an aliquot of whole EDTA-treated blood is also saved. All biospecimens are stored at -80ºC at the Moores Cancer Center. We will use state-of-the-art Next Generation Sequencing techniques to conduct targeted, aging-associated DNA

methylation profiling, including bi-sulfite sequencing and Illumina Mi-Seq.[68] DNA isolation from whole blood and methylation profiling will be conducted in participant-matched batches, i.e., all samples from a given participant will always be treated together. Methylation profiling will target validated loci whose level of methylation is associated with chronological age, which can be accelerated in cancer, and cancer risk and which are impacted by lifestyle behaviors.[68-72] The target loci are located in or near genes that regulate mechanisms of aging and cancer.[68-72]

Additional measures from the ActiGraph, 3-minute step test, and sit-to-stand test will be used to assess a dose-response relationship between changes in physical activity/fitness and changes in processing speed and self-reported cognition. The ActiGraph GT3X+ is used to measure minutes of moderate to vigorous physical activity at baseline, 3, 6, and 12 months. For 7 days at each assessment point, participants wear the ActiGraph on the hip during waking hours. The ActiGraph GT3X+ provides second-by-second estimates of activity that can be categorized into minutes spent in sedentary, light, moderate, and vigorous activity using calibration thresholds.[73] Its ability to measure physical activity with fidelity has been validated against heart rate telemetry and total energy expenditure.[74,75] Sufficient wear-time is defined as 5 days with ≥ 600 minutes of wear time or 3000 minutes (50 hours) across 4 days. Time spent in sedentary, light, moderate and vigorous physical activity is derived using published, standardized cut-points.[73] We are using the ActiGraph to measure change in physical activity and not the Fitbit because: 1) participants cannot be blinded to Fitbit data, which would likely impact the baseline assessment; 2) Fitbit uses a proprietary scoring method to classify physical activity as light, moderate, and vigorous that is frequently modified, which would impact measurement consistency over the course of the intervention; 3) ActiGraphs are the gold-standard objective measure of free-living physical activity, which will aid in comparison of results to other studies; and 4) the Health & Wellness Group does not receive Fitbits. The 3-minute step test is used to assess cardiopulmonary fitness. Participants are asked to step up and down on a 12-inch step at a constant pace (24 steps per minute) for 3 consecutive minutes. After a 5-second recovery period from stepping, the participant's heart rate is measured for 1 minute. This test of post-exercise heart rate has high reliability and sensitivity to change.[76] Lower-body strength is estimated via the 30-second sit-to-stand test. Participants are asked to stand up from a seated position as many times as they are able in a 30-second time period. This measure has good validity for measuring lower body functional muscle power and has been shown to be sensitive to intervention effects.[77]

Since cancer treatments can impact memory, executive function, and attention, these cognitive domains are also measured at baseline, 3, 6, and 12 months. Tests from the NIH toolbox cognition domain and the recommended measures by the International Cognitive and Cancer Taskforce (ICCT)[78] are used. For each domain, the individual test scores will be transformed into z-scores and combined to create a combined score. The National Adult Reading Test is administered at baseline as a measure of crystalized ability and will be used as a covariate in analyses. See Table 2 for full list of measures.

Primary Aims	
Objective Processing Speed	Oral Symbol Digit Test from the NIH Toolbox Cognition measures[64,65]
Self-reported Cognition	PROMIS Cognitive Function Measure[66]
Secondary Aims	
Psychological Mechanisms	PROMIS Anxiety, Depression, Fatigue, and Physical Functioning Measures for Cancer Survivors[67]

DNA methylation age	Aging-associated DNA methylation profiling, including bi-sulfite sequencing and Illumina Mi-Seq[68]
Dose-Response	
Physical Activity & Fitness	7-day, waking hours, hip worn ActiGraph GT3X+,[74,75] 3-minute step-test,[76] 30-second sit-to-stand test[77]
Other relevant measures	
Height & weight	Digital scale & stadiometer (height baseline only)
Demographics (baseline only)	Age, education, income, race, and marital status with standard surveys
Clinical	Chart reviews for date of diagnosis, stage at diagnosis, cancer treatments, date of end of active treatment, hormonal therapy, ER, PR, and HER2 status, and current medications. (baseline only) Self-report of medical history (baseline and 12 months only)
Memory domain	Hopkins Verbal Learning Test-Revised,[79] NIH Toolbox Picture Sequence Memory Test & List Sorting Working Memory Test[65]
Executive Functioning domain	Trail Making Test[80] & NIH Toolbox Dimensional Change Card Sort Test[65]
Attention domain	NIH Toolbox Flanker Inhibitory Control and Attention Test[65] & Conners' Continuous Performance Test 3 (CPT-3)[81]
Crystalized cognitive ability	National Adult Reading Test[82] (baseline only)
Quality of Life	PROMIS Sleep-related Impairment[83] and General Self-efficacy;[84] Cognitive and Affective Mindfulness Scale-Revised[85]

Table 2. *I Can!* study measures. All measures are collected at baseline, 3, 6, and 12 months, excepted where noted

7.0 Data analysis

We will summarize baseline characteristics and assess if randomization achieved balance by comparing distributions of key baseline covariates (demographics, baseline physical activity, baseline objective and self-report cognitive outcomes, cancer treatment, and related variables) between treatment groups (Exercise group vs. Health & Wellness group) using graphical methods, non-parametric and parametric tests as appropriate (e.g., Wilcoxon tests for non-Gaussian data, chi-square tests for categorical variables). Given the multiple cognitive domains, psychological factors, and biomarkers to be tested, we will use a Holm's sequential rejection test to adjust for multiple comparisons in all analyses.[86] We note that in our sample size estimates, we used a Bonferroni correction, which is likely conservative since the outcomes will be correlated.

To test efficacy of the treatment we will use a mixed model paradigm. For the primary aim, cognition scores at 3- and 6-months will be the repeated measures dependent variable; fixed effects will include baseline cognition, treatment group, time. A subject-specific intercept will be included to account for within-subject correlations. A statistically significant coefficient for treatment will indicate that follow-up cognition scores differed between arms. We will also examine group differences in change scores, by incorporating baseline scores in the repeated measures outcome, and including a group*time interaction term. This analysis will be conducted for objective processing speed and self-report cognition (Table 2). We will explore potential

moderating effects of key variables (e.g., age, time since cancer diagnosis, cancer treatment) on the association between treatment and objective and self-reported cognitive outcomes, by including the potential moderator, as well as 2- and 3-way interactions between the moderator, treatment and time. To test if intervention effects are sustained at 12 months (*Secondary Aim 1*), we will include baseline, 3, 6, *and* 12 month cognition scores, as the dependent variable and repeat the above analysis. By using appropriate contrasts, we will compare changes in cognition from baseline to 12 months (sustained treatment effect) or 6- to 12 months (maintenance of treatment effect) within- and between- groups. This mixed model approach will also be used for the additional cognitive domains, i.e., memory, executive function, attention (*Exploratory Aim 2).*

For Secondary Aim 2, we will test if the psychological and biological variables (M) mediate the association between treatment (X) and cognition outcomes (Y) using multilevel multiple mediator models[87-89 90]. Total, direct and mediated effects of X (and M) on Y can be derived from these models. To assess the robustness, we will apply bootstrap methods[91] to resample and refit mediation models to evaluate consistency of results. This analysis will be conducted for objective and self-report cognition.

Finally, to estimate a dose-response relationship between change in physical activity (via ActiGraph and/or 3-min step test) and cognition (*Exploratory Aim 1),* we will use generalized additive mixed models (GAMMs), which can accommodate a variety of distributions (e.g., positively-skewed physical activity data), account for dependency in error terms due to clustering (repeated measures), and estimate complex, dose-response relationships of unknown form.[92]

To assess COVID19-related protocol adjustments, we will conduct a sensitivity analysis by adding a binary variable (and its interactions with treatment, time) to models, to indicate whether an assessment was in-person vs remote. Although due to our RCT design, we expect that both arms will be similarly affected by these protocol changes, we believe it is a valuable opportunity to quantify the impact of mode of assessment on study results.

Sample Size and Power

We estimated the needed sample size for the Primary Aim, i.e., to compare differences in neuropsychological outcomes between the treatment and control groups over 6 months. We assumed a 2-sided test with a significance level (alpha) of 0.05/2 to account for two outcomes, i.e., objective processing speed, and self-reported cognition. We used means and standard deviations from randomized controlled trials including our pilot trial with breast cancer survivors as well as other studies with older adults[93-96] to guide anticipated effect sizes for the proposed intervention. Also, correlations on repeated measures of the cognitive tests ranged from 0.5 to 0.9 in our previous study; we used a conservative value of 0.5 in the present power calculations. Under these assumptions, with 110 participants per group, there is 80% power to detect a 0.3 standardized mean group difference in changes (i.e., effect size) in post-treatment cognition scores (at 3 and 6 months), adjusted for baseline scores (i.e., ANCOVA model). Using SD estimates from our previous work, this effect size corresponds to intervention-related mean group differences of 3.3 units in processing speed, and 2.5 units in self-reported cognitive abilities. If we also included the 12-month time-point (Secondary Aim 1), we have 80% power to detect a smaller 0.27 effect size corresponding to mean treatment differences of 3 units in processing speed, and 2.3 units in self-reported cognitive abilities over 12-months.

Allowing for a 10% attrition rate at 12 months (6% attrition achieved in previous 6-month trial with 333 breast cancer survivors), we aim to recruit a total of 250 participants to our study.

Missing data

Our analytic approach using mixed models[97] will yield unbiased results even if some observations are missing, as long as the data are "missing at random," i.e., the reasons for missingness can be predicted from observed measurement.[98,99] This assumption has been tenable in our previous studies, and we expect this to be the case in this study. However, we will conduct sensitivity analyses to test for informative drop-outs[99] and develop alternate approaches, e.g., pattern-mixture models, if needed.[100-102]

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